A SYSTEMS APPROACH TO THYROID HEALTH CARE

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CONTENTS

Abstract

This thesis examines the role of mathematical models in the management of patients with chronic thyroid disorders The major benefit arises from the ability of a model to integrate large quantities of biochemical and clinical data into a simple statement of expectation and uncertainty about the current state of a patient and likely developments. The immediate application of modelling is to the assessment and selection of tests or treatment to be applied to the individual patient. However, the provision of data in a form suitable for modelling introduces a data base which may be used for longer-term objectives. A sizable "routine" data-base can provide an important source of new information for modelling and allow a realistic assessment of tests and treatments over periods of time or groups of patients which would not otherwise be possible.

On the basis of a comprehensive systems analysis, an approach to more effective patient care is shown to involve enhancement of the role of the laboratory. Rather than act as a simple, positive, "instrument-at-a-distance", the laboratory should take a more active role in transforming raw clinical and biochemical data into useful information for clinical decision making. In such a system the physician remains the decision maker but the laboratory acts as an intelligent archivist and integrator of data.

The results of a pilot study are examined to determine the acceptability and usefulness of collecting a limited amount of clinical data. An attempt is made to tackle directly the immediate problem of selecting tests in thyroid disease. Although benefits can be shown from the use of chemical data it becomes clear that this is of limited value. The major constraint appears to be the absence of time series data.

The benefit of long-term feedback from routine requests collected for modelling purposes is examined and an attempt is made to show that it provides an accessible and intelligible, though limited, data-base on thyroid patients. An important point is that the data represent the population of patients seen by the laboratory, not by the physician who tends to act as a "filter". This means however that the data can only be a starting point for epidemiological surveys.

The clinical application of existing comprehensive models of thyroid function is examined highlighting the need for more limited model structures appropriate for the specific clinical problem. Data

from twelve thyrotoxic patients are used to identify a reduced clinical model. The distinct components of thyroid, pituitary and "peripheral" tissue are identified with varying degrees of success. A simple model of the thyroidal response can be identified even with a small number of measures with discrepancies between prediction and data of the order of the measurement error. The model appears to be a particulary effective method of drawing attention to unusal or anomalous results . Problems remain, however, with pituitary modelling and the extension of identification to sequential estimation. These dificulties are discussed and to demonstrate the feasibility of clinical and laboratory application the thyroidal model has been implemented upon a micro-computer. This model based approach offers aids to both the operation of the clinical chemistry laboratory and the physician during decision-making required in routine patient management.

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CHAPTER 1

Introduction

This thesis is an argument for the use of mathematical models and control techniques in the management of patients with chronic disorders. The major benefit arises from the ability of a model to integrate large quantities of biochemical and clinical data into a simple statement of expectation and uncertainty about the current state of a patient and likely developments. The immediate application of modelling is to the assessment and selection of tests or treatment to be applied to the individual patient. However, the provision of data in a form suitable for modelling introduces a data base which may be used for longer-term objectives. A sizable "routine" data-base can provide an important source of new information for modelling and allow a realistic assessment of tests and treatments over periods of time or groups of patients which would not otherwise be possible.

Though the work presented here has concentrated upon aspects of thyroid health care the approach would seem appropriate for the management of a wide range of chronic disorders. Many of the theoretical concepts used are well established and the aim of this thesis is to show that these ideas can be progressively introduced into health care largely by the exploitation of existing equipment and expertise. As a consequence most of the work is directed towards implementation of a medically acceptable system.

1.1 The Problem

The basis of medical knowledge is clinical experience. Every treatment and test must find its final validation in the continuous trial of clinical practice. Ideally, this experience is preserved in the medical record. In practice data are difficult or impossible to retrieve from this record even for those originally responsible for writing it and the record becomes a dump or at best a "leaky" store rather than the formal basis of knowledge. Each day sees many hundreds of costly results and clinical observations disappearing into medical records. Attempts to structure and bring "on-line" this voluminous,

complex (or haphazard) and varied collection of data en masse have been unsuccessful. A massive investment in time and money could transform this picture but is unlikely to be directed towards the management of "chronic" disorders.

The physician, often already uncertain of the value of existing biochemical tests, is required to understand a changing and steadily increasing range of biochemical procedures. Uncertainty encourages the physician to request a battery of tests which then must be interpreted. At times the physicians seem unaware of the basic imprecision of even common measures. Elion-Gemtzon (1980), for example, reported that the expected errors in plasma calcium measures exceeded the values on which the physicians receiving the results would normally take action. This problem is not uniform, of course. The specialist receiving dozens of results from a laboratory, perhaps from the same assay procedure or instrument each week may have an excellent idea of the clinical significance of a result, while others receiving only the occasional result have a much poorer impression. Augmenting the "normal range" with an estimate of test precision, either as a standard deviation or as confidence limits, has not been well received. This is partly because the physician is required to make a decision on the basis of a number of different measures or a sequence of measures over time. The problem becomes extremely difficult when a number of tests, whose accuracy may vary between types of test, or even between measures by the same test are to be examined at once (whether or not an estimate of accuracy is supplied). One simple aid is to plot out the confusing columns of data together with normal ranges, errors and treatments to give a pattern of behaviour over time. The natural extension of this process is to use a model to integrate objectively this mass of data and confirm trends or quantify treatment effects.

The laboratory is conscious of a steadily growing work-load both as existing tests are requested with increasing frequency and as new tests are introduced. At the same time doubts arise as to the clinical value of many of these routine measures. Clinical data presented to the laboratory are often sparse or of poor quality thus effectively limiting the laboratory role in test selection or interpretation. This tradition of the physician as the co-ordinator of patient information is difficult to challenge because of the simplicity of its organisation. At the same

time the physician frequently expects the laboratory to be a "centre of excellence" and seeks information on difficult or borderline cases, although this is usually restricted to problems with single measurements. One consequence of this separation between clinical practice and the biochemical instrument is that the increasing laboratory concern with quality control may not benefit the physician. A "perfect" instrument, as established by intra-laboratory quality control, may be irrelevant to the clinical reality of sampling error, intra-patient variability, drug effects etc. Instrument error is not simply summarised by the accuracy (bias and precision) observed in the few laboratory quality-control samples included. The "occasional" outlier or the patient sample which differs from the calibration samples used can be of far greater clinical consequence than a shift in overall precision of 1 or 2 percent. This does not deny the need for laboratory quality control but argues that the laboratory should take a more active role to establish and improve the clinical value of the information it provides.

1.2 Thesis Structure

Chapter 2 establishes the required background information on thyroid health care. The familiar regulatory model of the thyroid-pituitary axis is examined and the physiology and disorders of the individual components described. The conceptual model introduced here will be invoked in the later chapters on metabolic and clinical modelling.

Chapter 3 reviews the problems discussed above and proposes as a partial solution, the enhancement of the role of the laboratory. Rather than act as a simple, positive, "instrument-at-a-distance", the laboratory should take a more active role in transforming raw clinical and biochemical data into useful information for clinical decision making. In such a system the physician remains the decision maker but the laboratory acts as an intelligent archivist and integrator of data.

Chapter 4 describes the results of a pilot study to determine the acceptability and usefulness of collecting a limited amount of clinical data. An attempt is made to tackle directly the immediate problem of

selecting tests in thyroid disease. Although benefits can be shown from the use of chemical data it becomes clear that this is of limited value. The major constraint appears to be the absence of time series data.

An additional argument of this thesis was the benefit of long-term feedback from routine requests collected for modelling purposes. In chapter 5 an attempt is made to show the potential benefits of an accessible and intelligible, though limited, data-base on thyroid patients. An important point is that the data represent the population of patients seen by the laboratory, not by the physician who tends to act as a "filter". This means however that though the data can only be a starting point for epidemiological surveys.

Chapter 6 returns to the main theme by examining the clinical applicability of existing models of thyroid regulation. An attempt is made to extend these metabolic models by identifying additional structures and including behaviour in dysfunction. A comprehensive model suitable for use with routine clinical data does not seem possible given the information currently available so an attempt to produce a more limited model for a particular clinical problem follows.

In chapter 7 data from twelve thyrotoxic patients are used to identify a reduced clinical model. The distinct components of thyroid, pituitary and "peripheral" tissue are identified with varying degrees of success. A simple model of the thyroidal response can be identified even with a small number of measures with discrepancies between prediction and data of the order of the measurement error. The model appears to be a particulary effective method of drawing attention to unusal or anomalous results . Problems remain, however, with pituitary modelling and the extension of identification to sequential estimation. The dificulties are discussed in chapter 7 but to demonstrate the feasibility of clinical and laboratory application the thyroidal model has been implemented upon a micro-computer.

The thesis finishes with a brief summary of the important conclusions and prospects for further work in chapter 8.

CHAPTER 2

A Control Model of Thyroid Function in Normal and Unwell Patients

This chapter presents a systems view of thyroid physiology and disease in man. The first sections (2.1 to 2.5) introduce the general concepts of normal regulation and provide a framework for the more detailed descriptions of the physiology and disease states which follow. The aim is to set the relevant medical and biochemical information in a control system context which will be used for the subsequent analysis and modelling. As the application is medical, there is a greater emphasis upon the abnormal conditions and their treatment than is usual in the modelling of thyroid hormone regulation. Before introducing the thyroid model a short account of the general approach taken is given.

2.1 Models of Metabolism and Patient Behaviour

Models attempt to describe complex phenomena by the interaction of a number of simpler relationships expressed as laws, hypotheses or more general concepts. A satisfactory model must not merely reproduce observations and include previous knowledge but it must also satisfy the particular requirements for which it was derived. "Scientific" modelling is usually analytic and seeks to "explain" the observation made or the experiment undertaken. An "engineering" application may be less rigorous in the demand for homomorphism between model and reality so a "parsimonious" description for the prediction of behaviour may be all that is required. Occasionally where models emphasising both of these aspects are used simultaneously, such as a detailed model of a process combined with a simple input-output-plus-noise model to describe the instrumentation which measures the process states, the representation is perhaps more complex than the process itself. Three types of model can usefully be distinguished: descriptive, predictive and explanatory. Their relevance to the medical and metabolic modelling undertaken here will be briefly outlined. A more comprehensive discussion appears in the review by Carson et al (1980).

A descriptive model seeks to replicate observations by the interactions of a simple set of relations formalised in its structure. The basic diagnostic model is of this type: seeking to ascribe classes or disease states according to the re-occurrence of similar sets of symptoms and pathologies and thus generating a simple taxonomy of the diseases. This can be largely independent of any knowledge of the underlying biochemical process. To be of use this formal description must be extended to cover future events by assuming stability of behaviour over time and between samples of patients. The predictive model is then "comfirmed" by continued observation of the system. In this way the diagnostic model might be considered predictive if the initial observations could be assumed to be sufficient to predict subsequent states or behaviour. A direct example would be a model of patient responses to therapy. Here, previous treatment responses are taken to be predictive of subsequent behaviour under similar conditions. These models are frequently based solely upon limited empirical data rather than a systematic reduction of a more complex, but well established, structure to retain only those components relevant to the model purpose. These 'empirical' models based upon limited data are often unsatisfactory because of unknown or unconsidered inputs, or because they attempt to include observed complexity by ad hoc additions. Medical models tend to be empirical as they are traditionally drawn from medical experience and records. They are frequently vaguely formulated and descriptive or predictive in purpose. Metabolic models, however, tend to include more prior structural knowledge and usually have the aim of hypothesis testing or the quantification of an explanatory model by additional measures. In the modelling undertaken in this work, an initial purely descriptive statistical formulation was followed by an attempt to develop as far as possible a metabolic model of thyroid regulation. This detailed model was then reduced to match the requirements of the physician. It is convenient to introduce at this stage the general concept of regulation and some of the other basic elements of this modelling.

2.2 Regulation and Hormonal Control

The notion of an actively maintained equilibrium, termed homoeostasis by Cannon (1929), as a basis for the characteristic stability of living forms against developmental or environmental

disturbances, is now a familiar term in physical description. Ideas of information and control which can begin to explain the complexity and resilience of these organisms are discussed by Yates (1981), together with some of the limitations of this approach.

The presence of minute quantities of compounds which instigate considerable changes in cellular function - usually to resist or assimilate disturbances or to control development - were quickly identified as chemical control signals. These hormones are complex proteins, often synthesised in specialised endocrine cells and transported to target tissue by direct diffusion or via circulation. The model commonly invoked to describe hormonal control is simple regulation (figure 2.1). This considers the system to consist of a plant and controller with a single negative feedback loop. The structure may be extended, at least conceptually, by further loops, by interaction or competing controllers perhaps at different levels, which may be organised into a hierarchy. These models assume the reducibility of the biology so the elements or components can be described by relatively simple, and preferably linear, relationships. To be used for even the most limited of predictions, these elements must allow confident interpolation and, probably, some degree of extrapolation from the necessarily limited measurements. Much of the power of statements in chemistry or mechanics lies in confident assumptions which can be made about the collective behaviour of large groups of particles. In biology where controller and plant have evolved together and so are difficult to distinguish, where signals and products may both refer to a few particles undergoing low energy transformations in a richly connected environment there is far less confidence in these simple and sweeping assumptions.

It is often difficult to establish that the measures available are appropriate to the conditions the model is to represent. Measures made in vitro or in vivo with unphysiological inputs may give rise to correspondingly unphysiological results. A typical example might be the changes in rate of an enzyme process. Figure 2.2 represents the complete signoidal characteristic of a process depending upon some activation agent or hormone. If changes in the agent are confined to small perturbations, particularly about a working point in the linear region, then a simple linear relationship would be observed. Changes

taking the system outside this limited region would, however, require a non-linear relationship, perhaps of the switching or catastrophic type. A single process might exhibit either mode, depending upon input or local conditions. A recent general discussion of the significance of these chemical transducers together with a number of examples has been given by Koshland et al (1982). Clearly the small-perturbation models commonly employed in metabolic modelling are likely to be of limited explanatory value and unlikely to be appropriate in abnormal states. This is exactly the problem encountered when attempting to use metabolic models identified under normal conditions to patients who are by definition "abnormal".

A final problem is the tendency to divine purposes and functions, drawn from experience in other fields, in biological systems. While it is tempting to propose that the purpose of the thyroid, for example, is to regulate thyroid hormone levels, care is needed with such interpretations. Most biological structures have evolved under constraints quite distinct from those applied in engineering and probably do not reflect any kind of "optimal solution". Natural systems develop under the considerable limitation that they cannot be taken "off-line": all intermediate forms must be viable on the progression towards an optimum. It has been suggested that new concepts of value to engineering may arise from the study of living systems. This seems correct in the long term: biological systems clearly have facilities that no engineering systems possess, but in the short term it would appear that the flow of ideas is in the opposite direction. Given the constraints above, an abstraction will always be realised first in an artifact then "recognised" in the natural system. It would be useful to consider this outline of the approach taken and its limitations when applying it to the description of the thyroid-pituitary axis in man.

2.3 Thyroid Hormone Regulation in Man

The thyroid gland is assumed to have evolved to ensure a reliable and consistent supply of the two hormones thyroxine (T4) and triiodothyronine (T3) both of which include the rare element iodine. The dietary sources of iodine show considerable variations which are largely related to local geological deposits of the element. Thyroid hormones are required for life, but their action appears to be one of

maintenance of steady energy usage by cells. The basal metabolic rate is sensitive to changes in the level of the hormones but apart from minor shifts in illness or starvation there appears to be no condition which requires changes in hormone levels. Indeed it is not clear whether these hormones should be viewed as signals, as controlled substrates or as triggers for the cellular energy process. Other hormones such as insulin or noradrenaline have an obvious signalling action as relatively small changes in their concentrations can trigger much greater energy or transport effects. Irrespective of these qualifications, it is clear that thyroid hormone levels must normally be kept constant to ensure well-being.

The thyroid, which is the largest of the endocrine glands, is richly vasculated and acts as a trap or filter of plasma iodine and as a store of the two iodoproteins, (T4 and T3) and their precursors, which are capable of sustaining hormone output for several months of iodine deficiency. The gland may be considered as a plant for the uptake of new or recycled iodine, the production, storage and finally controlled release of these iodoproteins. Control of the gland is exercised by the anterior pituitary via the release of thyrotrophin (TSH), a thyroid stimulating hormone, into the plasma. Regulation is obtained by the comparison of thyroid hormone levels with an internal "set point" obtained in turn from a hypothalamic thyrophin releasing hormone (TRH). An increase in thyroid hormone levels reduces TSH release while a fall is associated with an increase in TSH levels. This is the basic concept of thyroid hormone regulation as shown in figure 2.3. The stimulus for TRH release is assumed at present to be the central nervous system alone, though there is evidence for a direct action of thyroid hormones upon the hypothalamus (Belchetz et al , 1978) Further feedback loops are considered possible, particularly involving the hypothalamus, but this remains uncertain until measures of TRH improve.

The two thyroid hormones are released into the plasma where they bind strongly to circulating proteins. Their metabolic action requires transport through cell membrane which is dependent upon the residual free fractions of the hormones. The plasma proteins have a buffering effect, as the binding considerably increases the available hormone without increasing the free concentration, and so stabilises hormone levels against short-term fluctuations. T3 has a lower binding affinity

than T4, so the total plasma ratio of the two (T4/T3) is approximately 20 while the ratio of the active free fractions is approximately 2. Clinical responses suggest that T3 is about three times as effective as T4 after infusion. In most peripheral tissue, but particularly liver and kidney, T4 is deiodinated to T3 or the inactive metabolite rT3 (reverse T3). Evidence suggests that both T4 and T3 act directly upon tissue but in the event of iodine lack or hyper-stimulation of the thyroid cells, T3 is produced in preference to T4 so conserving iodine. Normally, however, peripheral conversion from T4 is the major source of T3 so unidirectionally linking the more volatile T3 concentration to the slower T4. Deiodination to T3 or rT3 is assumed to be random and dependent upon the free T4 concentrations but there are suggestions that local control of deiodination enzymes to maintain T3 levels may occur.(Cavalieri and Rapport (1977))

2.4 Measures of Thyroid Regulation

The clinical signs of thyroid dysfunction, though obvious in extreme cases, are often insufficient to make a diagnosis: the problem being greatest in the aged. The heavily damped characteristics of thyroid regulation, the often slow onset of the underlying disease and individual variations in tissue sensitivity, which mean that the full range of signs may never appear, are probably responsible for these problems. The system naturally resists the effects of individual failure so "mild" conditions can persist for considerable periods and it is uncertain whether these marginal dysfunctions have long-term clinical effects. It is clear, however, that general disability is associated with progressive failure and that early treatment inhibits the appearance of the more extreme symptons.

These difficulties have encouraged research into biochemical measures of thyroid regulation, but to date no direct measures of cellular effects are available and only plasma concentrations can be obtained. The thyroid gland is the most common site of failure and consideration of the regulatory system of figure 2.3 would suggest that the changes in the pituitary error signal (TSH) would be the most useful single measure. Knowledge of plasma TSH levels would give an amplified version of the thyroid hormone error perceived by the pituitary thyrotrophs which compare intracellular hormone levels with the

hypothalamic demand expressed through TRH levels. This would automatically include most interfering factors such as changes in binding protein levels and variation in individual tissue sensitivity and give the physician a good basis for treatment. The TSH response to changes in thyroid hormone levels is strong, showing a greater than exponential growth with falls in T4 or T3 levels, but the assay for TSH is insuffiently sensitive to distinguish between normal and low TSH levels (hyperthyroidism). The TSH test is, however, a good discriminator of normal and high levels (hypothyroidism).

The diagnosis and treatment of hyperthyroidism requires the measurement of plasma T4 and T3 concentrations. Assays of total plasma T4 and T3 may be augmented by an estimate of plasma protein binding (RT3U,TBG) to give an index of the free hormone levels (FT4I,FT3I) or at greater cost a true free measure can be obtained (fT4,fT3). The free estimates are required in some cases to exclude effects arising from changes in protein binding which can occur for a number of reasons including age, pregnancy or congenitally abnormal protein levels. T3, as the the more active of the hormones, follows the clinical state more closely, but total T4 levels are about 100 times greater so the T4 measure tends to show a better precision over a wider range than the T3. A further factor is the tendency of the stressed thyroid to produce relatively more T3 than T4. This means that in hypothyroidism near normal or normal T3 is sometimes seen with low T4 and raised TSH levels. Conversely in hyperthyroidism normal T4 and TSH levels may be accompanied by high T3 results (T3-toxicosis).

The three measures (T4,T3 and TSH) are the three routine assays currently available obtained from a single sample of blood. A number of dynamic tests can be used to assess the thyroid (T3 suppression, TSH stimulation, radioactive iodine turnover) or the pituitary (TRH stimulation) function but because they require a number of samples and an exogenous input are not routinely provided.

2.5 A Model of Thyroid Regulation in Man

A simple conceptual model is introduced at this stage to make explicit the relationships between the measures discussed in section 2.3 and the basic concepts described in section 2.2.

If the changes in relative production sites of T4 and T3 by the thyroid as it is stressed are ignored and the rate of T4 to T3 conversion assumed a constant, then the simple linear response shown in figure 2.4 can be obtained from the model outlined in figure 2.3. This steady-state response ignores the distribution dynamics of the thyroid hormones but is a useful representation which may be compared with routine clinical measures. In practice the T3 and T4 values observed depart from the simple linear form probably because the hyperstimulated thyroid tends to produce relatively more T3 than T4. The result is a rise in the T3/T4 ratio in both hyper and hypothyroidism. The lower T3/T4 ratio associated with patients on T4 replacement therapy is discussed in chapter 6. A more complete justification of this steady state model as a reduced form of a more comprehensive model of thyroid regulation is given in chapter 6. Figure 2.5 shows the relationship between TSH and thyroid hormone levels. This simple form arises because of the assumptions of linearity made about de-iodination and hormone release which also means that the plasma concentrations are directly proportional to the hormone release rate. It is assumed that thyroid hormone release rate eventually shows saturation with increasing TSH stimulation. The initial slope is the normal operational region and the slope at the operation point gives the effective thyroid 'gain'. Pituitary response almost certainly shows a similar saturation at high release rate (low thyroid hormone levels), but a simple exponential form of response to falling thyroid hormone levels is assumed. Perturbation studies examined by Saratchandran et al (1976) could not be replicated by the dynamics associated with this model. Instead, integral feedback to the pituitary had to be added to account for the observed TSH response. This suggests longer term effects upon the pituitary whether directly, through T3 or T4 stimulation or via the hypothalamus, perhaps upon protein synthesis. The result of clinical interest is the shift in the "load lines" of figure 2.5 as the stimulus continues over time. This gives rise to a family of curves which reflect this multiplicative action upon TSH output. The figure shows the shifting of the observed T3 and TSH levels (operating point) as the thyroidal output falls in primary hypothyroidism or rises in hyperthyroidism. Failure of the pituitary or hypothalamic output, known respectively as secondary or tertiary hypothyroidism, can be distinguished by the low TSH concentration.

This is the basic clinical model of thyroid regulation. An alternative view would be to stress the importance of iodine metabolism in a model of the iodine cycle but radio-iodine measures have been largely superseded and, apart from ablative radio-iodine therapy, iodine is not used in treatment. The following sections, 2.6 to 2.10, discuss the individual components of this model in greater detail.

2.6 Peripheral Effects of Thyroid Hormones

Severe variations of thyroid hormone levels give rise to clinical signs which are chronic, or slow, in their onset rather than acute. Deterioration continues at an increasing rate, however, until death occurs.

If the Basal Metabolic Rate (BMR) is measured by oxygen consumption the effects of thyroid hormones can be demonstrated after ingestion of either T4 or T3 . The delay before effects are seen and the slower, gentler action of thyroxine has been noted. (Nicoloff 1978) Although the influence is generalised, changes in particular tissues make diagnosis of severe hyper- or hypothyroidism straightforward. Problems arise in less severe failures where some symptoms may be mistaken, especially in the aged. It is also common that the individual tissue response either over-emphasises or fails to demonstrate typical signs. In the most subtle cases, constipation, cramps or anxiety may be the only presented signs. Clearly, therefore, the insidious onset suggests a progressive action in the tissue which shows considerable individual and inter-tissue variation.

There are no direct measures of intracellular hormone concentration. The indirect clinical measures are cumbersome (BMR, Ankle reflex) subjective and open to considerable observer variation. This explains the great preference for the more precise results of a biochemical measure of plasma hormone levels. The biochemical diagnosis must however finally rest upon the evaluation of clinical state by physician and patient. In this way a better correlation of clinical state with free hormone measures has been detected.

Bearing in mind the above difficulties of clinical assesment and individual variation, presumably reflected in hormone levels, attempts

have been made to locate biochemical measures dependent upon thyroid hormone levels. Currently, the only successful candidates are measures of pituitary response by basal TSH. The pituitary cells, when functioning correctly, are acutely sensitive to changes in thyroid hormone levels and a raised basal plasma TSH is probably the best indicator of hypothyroidism. Unfortunately low and normal TSH levels cannot yet be discriminated but stimulation of TSH release by TRH can be used to check for suppression of pituitary action during hyperthyroidism.

Abnormal states arising from changes in peripheral uptake or responsiveness to thyroid hormones are currently unknown.

2.7 Serum Protein Binding of Thyroid Hormones

In plasma, the hormones T4 and T3 bind reversibly and almost instantaneously with three circulating proteins. These three proteins (TBG,TBAb,prealbumin) have considerable capacity for binding hormone so normally there is no possibility of their saturation. A table of the proteins, their concentrations and the distribution of T4 and T3 according to a multiple binding model, appears in Prince and Ramsden (1977). The degree of binding is defined by the affinities of protein and hormone but as hormone is taken up competition occurs between T4 and T3 for the same binding sites and to some extent interaction between binding sites occurs. These interactions have not been fully resolved but the model used includes these factors as far as possible and suggests that subsequent modifications will be minor. Measurements of hormone level were initially of the total concentrations since the free fractions are extremely small. Subsequently it was shown that the free fraction was metabolically active and that a constant ratio of free to bound was not always maintained. As the protein levels rose (pregnancy, oestrogens) or fell (hepatic disorders, congenital lack of protein) with the total hormone levels following, the free concentrations, particularly of T3, tended to remain constant. As free hormone measures are only now being developed for more than exceptional use, an intermediate step was to correct the total measure by a factor determined by estimates of the binding capacity, the "Free Index". Using the results from the Prince and Ramsden model, the errors produced by using total hormone measures - as often happens in earlier data - in

cases of abnormal function or protein levels can be assessed. The model shows that in cases of high T3 ("T3 hyperthyroidism") levels, the free/bound ratio is almost unchanged. If, as is usual, T4 also rises then the percentage of free hormone increases. This effect is unlikely to be compensated for by increased output of TBG. This effect is about equal in each hormone so linearity is preserved.

The model by Prince and Ramsden is an extension of work by DiStefano and Chang (1971) who showed that a simpler binding model could be reduced to a polynomial function expressing the relationship between bound and free concentrations and then further simplified in normal man to a simple constant. The implications of Prince and Ramsden's work are that this simple ratio will show discrepancies for abnormal thyroid levels. The errors are nearly equal for T3 and T4 and depend upon increasing levels of T4. Estimates of T3/T4 ratios are unaffected. Care is needed only when considering effects of free hormones in abnormal states.

As was mentioned earlier, the binding of thyroid hormones considerably modifies their behaviour and these differences can be related to differences in binding affinity. The lengthy half-life of T4 and the shorter one of T3 reflect the weaker binding of T3. This difference means that only 10% of total plasma T4 is turned over daily, against 75% for T3. The consequent buffering effect means a doubling of T4 production taking twelve hours to increase plasma levels by more than 5%. It is therefore surprising that short-term fluctuations of TSH and total thyroid hormone concentrations have been seen as assay precision has increased. Circadian rhythms have been seen by Lucke et al (1977). This is unlikely to reflect true changes in hormone levels and probably reflects movements of proteins among plasma and fluid compartments during the day. Protein affinity differences mean that T4 is mostly found in liver, kidney, and plasma, while most T3 resides within tissue (muscle, skin, brain) which cannot be entered by large proteins. The study of hormone distribution and resultant kinetics has been extensive.

2.8 Peripheral Distribution and Disposal of Thyroid Hormones

De-iodination in tissue is the major route for the disposal of T4 and T3 and for T3 all products are inactive. The metabolites of T4,

however, are T3 and 'reverse' T3 (rT3) which is inactive. The T3 produced by this route accounts for up to 80% of the peripheral T3 and an even greater proportion of reverse T3.

Interest in T3 has developed since the demonstration that T3 and rT3 in some conditions show reciprocal changes in concentration. This leads to the suggestion that T4 de-iodination is not simply random and that some peripheral control of cellular T3 is possible. The evidence is found in certain systemic diseases and prolonged fasting when a fall in plasma T3 is accompanied by a rise in rT3 levels but no increase in TSH or signs of hypothyroidism. There are also reciprocal changes in infant T3 and rT3 before and after birth. Although some in vitro work implies inhibition of conversion by T3, no definite conclusions have been reached. The effect could be of clinical importance in T4 replacement therapy for hypothyroid patients indicating that plasma T4 is not a reliable indicator of state but that with some physiological control remaining this is not of major importance. This is examined in more detail in chapter 6.

Radioactive tracer work in man and sheep have led to a three compartmental model for hormone distribution gaining general acceptance (figure 2.6). Irvine et al (1974) have introduced a fourth compartment by separating plasma and extra-cellular fluid on the basis of work in sheep, but this has not gained support. Identification of the three compartments had been attempted by DiStefano et al (1975). The actual structure used (figure 2.6) is described by sixteen parameters and analysis showed that with inputs and measures confined to the plasma compartment it was not possible to identify the model fully. Assumptions about the size of the two tissue compartments allow this uncertainty to be reduced. Even then the relative contributions of the two tissue types to T4 to T3 conversion cannot be determined. More importantly, thyroid hormone binding to cellular receptors occurs in these tissues and effectively increases the compartment volumes.

A more important factor, introduced earlier, is the question of non-random peripheral T4 to T3 conversion. Apart from the medical problem of predicting the results of T4 therapy, any modelling of thyroid hormone release which includes the wide range of peripheral concentrations seen in abnormality rests upon the model of peripheral

conversion, since direct measures of secretion are unavailable. Current literature has been examined and is reviewed briefly below.

Mindoroni and Dimitriu (1976) estimated conversion rates on a simple plasma compartment from data on athyroid patients given T4 therapy. They state that the mean conversion rate is inversely proportional to serum T3 and the rate generally increases over time despite a falling plasma T4. Their conclusion is that an "adaptive" mechanism is required for conversion. Unfortunately the plasma T3 levels are not given and conversion does not seem to increase significantly with time.Their observation that the maximum plasma T3 followed three days after T4 input is supported by Wenzel et al (1975) who reported a 72 hour delay in T3 rise after oral T4 administration. It is possible that conversion occurs in the 'slow' tissue compartments which introduce the delay, but evidence from patients in hepatic failure (Green et al ,1977) suggests considerable conversion occurs in the 'fast' liver and kidney tissues.

It would seem a straightforward matter to test this possibility by giving euthyroid and hypothyroid subjects increasing doses of T4 and examining the plasma T3/T4 ratio but this does not appear to have been done. Observation of the routine T3 and T4 assays of patients at the Middlesex Hospital during two surveys reported in chapters 3 and 4, does suggest a deviation from the simple linear model of figure 2.4. As will be described in chapter 4 and discussed further in chapter 6, patients receiving T4 therapy often showed a lower T3/T4 ratio then untreated patients or those receiving Carbimazole (antithyroid treatment). A number of possible interfering factors were considered. The first was increased T4 measures because the patient had recently taken a tablet: but this should not cause such wide swings of plasma T4. The T3 or T4 assay is not linear: it is believed that hyperthyroid patients secrete relatively more T3 than T4 so the curve followed by the hypothyroid patients on T4 may correspond to an increasing bias in measurement. The hyperthyroid patients should then follow a more non-linear course with increases in T3/T4 plasma ratio. A final possibility is that conversion may indeed take time to adapt to changing hormone levels, so initially low T3/T4 levels would last only until the patient had adjusted to the new therapy induced hormone levels. There is no evidence of this in the literature however.

Felt and Nedvidkova (1977) showed a similar fall in T3/T4 ratio in treated hypothyroid patients while Burman et al (1976) did not. It may be possible to resolve this difference if the results of Burman et al have been obtained from patients where the T4 dosage has been carefully adjusted to the minimal to maintain euthyroidism while some of the groups studied by Felt et al are somewhat over-treated.

Schimmel and Utiger (1977) and Cavalieri and Rapoport (1977) both reviewed the peripheral conversion of T4 and reported on a number of factors. Conversion seems to rise twofold in hypothyroidism, though this could be masked by relatively increased T3 secretion, with conversion rate remaining constant in hyperthyroidism. Fasting leads within 24 hours to a fall in T3, raised rT3 and little or no change in T4 in the obese, normals and athyroids on T4 therapy. Age has been associated with significant falls in T4 and particularly T3. These reports, however tended to be based upon small samples of an often unwell group of patients. Evered et al (1978) presented an extensive survey showing only a slight fall in T3 levels. In hepatic cirrhosis, lowered T3 and slightly raised T4 levels (Green et al, 1977) suggest the importance of the liver for conversion. Normura et al (1975) obtained a 50% fall in conversion in such patients. Propylthiouracil (PTU) inhibits conversion and therefore has a peripheral antithyroid role and may be occasioally used in therapy.

Clearly the conversion of thyroid hormone in the periphery remains uncertain. Both possible versions, the linear conversion and the controlled conversion are therefore retained. Further work is necessary to distinguish the actual mechanism or at least to assist in the derivation of discriminatory experiments.

2.9 The Thyroid Gland

The thyroid gland weighing between 15 and 25 g in the adult is the largest endocrine gland in man. It appears as a flat bi-lobed structure lying either side of the larynx and trachea. The gland is well supplied with blood and consists of a series of vesicles, the thyroid follicles filled with a mucilaginous colloid. The colloid is surrounded by an epithelium composed of follicular cells responsible for hormone production, release and storage in the colloid. Occasionally a second

type of cell can be observed, the parafollicular cell which produces a hypocalcaemic hormone, calcitonin.

Four stages can be identified in thyroid hormone production (figure 2.7): the uptake of plasma iodine: iodination of the protein thyroxine and transport as thyroglobin into colloid: conversion of the thyroxines to T4 and T3: and finally protolysis of the thyroglobin and release of T4 and T3. De-iodination is known to occur within the thyroid and it is thought that this may be responsible for some of the T3, and all of the reverse T3 released from the gland. These are minor products anyway, T4 being the predominant iodothyroxine. The four stages of production are dealt with below in sufficient detail to suggest their significance for a clinical model of the gland.

Despite passive diffusion out of the gland an active transport mechanism concentrates a considerable amount of iodide. Transportation shows responsiveness to TSH and in vitro a short fall in uptake is followed, over four hours, by a steady increase in transport into the gland. TSH action on uptake is, therefore, unlikely to make any contribution to the immediate release of hormones seen after a TSH input. Iodide transport is also subject to cellular regulation and Sherwin and Tang (1974) have proposed a model in which TSH sets the maximum rate of uptake (Vm) and intracellular iodide the semi-saturation value (Km). Perchorate is an inhibitor of uptake which had found some application in treatment of hyperthyroidism.

Once within the cell, iodide is swiftly oxidised by thyroid peroxidase and taken up by thyrosine to form mono- and di-iodothyronine (MIT and DIT) depending or whether one or two iodine atoms are bound. These products are linked to thyroglobulin, a large protein of molecular weight 670,000, and move into the colloid. Iodination can be inhibited by drugs of which the most common are Carbimazole, Methimazole and, less frequently, Propylthiouracil (PTU). In vitro thyroid preparations show an ability to escape drug blockage unless a limiting concentration of drug is applied (Taurog ,1978 : Mortimer et al 1977) Perhaps surprisingly, large doses of iodine will temporarily reduce hormone production, but after some delay a transport adaptation occurs and as the intra-cellular concentration falls again iodination recommences. As these agents act before the storage of iodothyronines, release of the

stored thyroxines will continue, at a decaying rate, for some time. To relieve symptoms at once, other drugs may be necessary to block hormone effects at the peripheral tissues. PTU may be useful here because of its dual action on thyroid and on the conversion of T4 to T3.

By far the major product of the conversion of DIT and MIT to the thyroxines is T4, however when an iodine shortage occurs then T3 production is relatively favoured. This is presumably caused simply by the reduction of the DIT/MIT ratio as less and less iodide is available. It has been noticed that similar effects occur in the hypo- and hyper-thyroid gland and it is assumed that an 'iodide-sparse' condition holds for both. In hypothyroidism there is little iodide being taken up and in hyperthyroidism the stimulated gland uses up all the iodide absorbed. Stimulation by TSH also seems to favour T3 production. The release of thyroid hormones occurs immediately after the TSH stimulus. Colloid is engulfed at the apical membrane forming droplets which migrate down the cell shrinking and becoming more dense. The thyroglobulin is broken down together with MIT and DIT while the T4 and T3 , together now with traces of rT3, are released into the blood. Some thyroglobulin, MIT and DIT also seem to escape directly or via lymphatic drainage but most is de-iodinated and the iodide released may be used again.

Measurements of secretion rates cannot be made directly, however, Westgren et al (1977) have studied hormone concentrations in thyroid venous blood of patients undergoing surgery for the removal of the parathyroid glands. A concentration gradient can be observed which is reduced by T3 pre-treatment and can be increased by administration of 250 ml of TSH. Although figures are not given, the authors claim wide variations in concentrations measured in a single vein over the course of 60 minutes. This may imply that despite the averaging effect expected of secretion from a large numbers of cells, thyroidal output is extremely 'noisy'. This variable secretion rate could give rise to short-term oscillations ('ringing') perhaps seen as circadian rhythms if the distributional kinetics have the right time constants. The data from Westgren et al showing the thyroidal response to TSH are interesting. Instead of an immediate rise in thyroidal venous concentration which is then maintained or falls over time, there is a progressive increase. This presumably indicates, since peripheral plasma levels hardly change, that secretion rates follow a similar

course. The implication is that despite the decline of TSH concentration (half-life at the most 70 minutes) an integral rather than proportional effect is predominant and, as the rate of increase in output seems fairly constant, suggests that the TSH action is saturating the thyroid. Caution is required since the measures are from a single patient after T3 therapy and undergoing surgery at the time! Other data are necessarily indirect. Working from measurements of plasma levels after TSH stimulus means that changes, in T4 especially, are difficult to observe and interpret.

Inhibition of release can be obtained by administration of iodine or lithium but they are not used because of possible side effects and availability of alternatives.

It seems likely that there will be a considerable delay before the detail included in this description becomes the basis of quantitatively useful clinical models. Some aspects, however, can be examined, though the need to combine them into a comprehensive model does not yet arise. The action of the antithyroid drugs for example is a long-term effect which will probably not combine accurately with estimates of thyroidal response after TSH which is a short-term effect. A start can, however, be made and these elements included in a comprehensive conceptual model at least.

2.10 The Pituitary and Hypothalamus

The pituitary is a small gland some 1cm in diameter and of weight about 4 g but of great importance in man. It secretes major hormones which affect not only peripheral tissue but also the other endocrine glands. It lies just below the central floor of the brain, known as the hypothalamus, to which it is linked by a short stalk of tissue. The gland develops in the foetus from two distinct tissue types. An outcrop of the hypothalamus forms the neuro-hypophysis or posterior pituitary. Epithelial tissue migrates to form the adenohypophysis or anterior pituitary. These and a third intermediate tissue remain distinct regions within the pituitary and while the posterior is clearly linked by nerve cells running down the stalk from the hypothalamus the anterior lacks an obvious link. Instead control of the anterior cells is believed to be mediated by hormones produced in the hypothalamus. These

neurohormones are carried by hypothalamic-pituitary portal vessels into the pituitary.

Within the anterior pituitary lie the thyrotrophic cells which, like other pituitary cells, appear to have become specialised for the production of a single hormone (TSH). The thyrotrophs typically contain a single row of hormone-rich granules adjacent to the plasma membrane with smaller granules lying deeper into the cell. Unlike the thyroid then, there seem to be no special structures for storage of the hormone.

The hypothalamus contains a large number of neuro-secretory cells and this area of the brain is involved in a wide range of nervous stimuli. When a particular area of the hypothalamus is excited by an electrical stimulus thyrotrophin-releasing hormone (TRH) is secreted. Adjacent to the active hormone-secreting areas are centres associated with temperature control and hunger. It is tempting to see the changes in thyroid hormone arising in fasting and systemic illness as an adaptive change instigated by the hypothalamus. A lowering of TRH and therefore TSH levels could result in a change in thyroid secretion tending to reduce T3 output. Against this proposal is the evidence that similar changes are observed in patients on thyroid hormones and therefore independent of thyroid output.

While measurements of TSH in plasma have been possible with slowly increasing precision for many years, the assay of TRH has proved extremely difficult. In part this is because of the short half-life of TRH in plasma, of the order of 5 to 6 minutes. These peripheral measures of TRH may prove to be of limited value since TRH is found and produced throughout the brain so plasma TRH may not be of entirely hypothalamic origin. Nevertheless, using an assay for plasma TRH, Mitsuma et al (1976) have assessed various clinical conditions and produced a coherent set of results. TRH levels appear to be raised in hypothyroidism and lowered in hyperthyroidism, in step with TSH levels, and to revert to normal during the course of treatment. The concentration of TRH will be higher in the pituitary than in plasma as the TRH has not yet been distributed throughout the plasma volume. This means that quite high inputs of TRH are required, when compared with measured plasma concentrations, before a significant TSH output is observed. The volume of distribution for TRH is uncertain since the

plasma measures remain unconfirmed but the data presented by Schimmel and Utiger (1977) suggest an initial volume of distribution of about 10 litres. Utiger (1978) goes on to mention earlier work on the appearance of TRH-like substances in urine after injection of TRH which suggested two compartments, but reported doubts over the specificity of these urine determinations.

Originally TRH was thought to release only TSH but it has now been shown that prolactin release also occurs after TRH and like TSH it can be blocked by thyroid hormones and enhanced by oestrogen. A distinct prolactin-releasing factor has now been separated from TRH although it is thought that this releasing effect is of secondary importance. Apart from these measurements, the understanding of hypothalamic-pituitary action has had to rely upon indirect assessment via TSH measures. These have implied an exponential relationship between 'steady state' thyroid hormone and TSH plasma levels (Larsen ,1978). A second order response for the pituitary after a bolus injection of TRH, (the TRH stimulation test), but a biphasic response after a continuous TRH stimulation (Wartofsky, 1976). Finally there is a marked depression of TSH output after pretreatment with exogenous thyroid hormone. Unfortunately these observations do not separate the different roles taken by pituitary and hypothalamus.

There is evidence for a direct negative feedback action of both thyroid hormones on the pituitary: the in vitro response of pituitary cells to TRH can be blunted by both T4 and, more strongly, by T3: in vivo in animal studies after a sharp reduction in TSH output caused by hypothalamic lesions, pituitary sensitivity to thyroid hormones is retained, but at a reduced level. Apart from the TRH measures in disease, mentioned earlier, micro-injection of T3 into the hypothalamus of thyroidectomised, and therefore hypothyroid monkeys, shows a complete though transient cessation of TSH output. (Belchetz et al, 1978). Injection directly to the pituitary had no effect on the small quantities used and injection of solvent showed that the response was not initiated by damage. These and other results have led to discussion of a second thyrotrophin-inhibiting factor, and somastastation (growth hormone release inhibiting factor) seems the most likely candidate. This remains a matter of conjecture, however. It seems likely that the original notion of the pituitary responding to thyroid hormone feedback

with its 'comparator' set by TRH will be retained. The TRH set point can indeed be modified but despite the rapidity with which TRH could respond it is probably only progressively altered after an error is seen to persist in thyroid hormone levels. The distribution volume of TSH is usually taken to be coincident with the plasma, though the volume estimated seems nearer to 4 litres than 3. One study to estimate turnover demonstrated a second compartment but the equipment had involved raising TSH concentrations to an extremely high level and it is difficult to know if these non-physiological conditions affcted the results. Secretion by the thyrotroph is commonly tested by the TRH stimulation test. If the TRH input is maintained, a new higher level of TSH secretion is achieved, the dynamics suggesting an immediate release followed by slower protein synthesis effects. The thyroid hormone inhibitions take several hours before becoming effective. This was included as a pure delay of 48 hours in the Saratchandran model. The reduction in output after repeated or continuous TRH challenge seems to represent the exhaustion of local intracellular TSH stores and the later output to reflect the rate of hormone synthesis.

2.11 Disorders of Thyroid Regulation and their Treatment

In this section the overall effects of disorders of regulation are considered using the model described in section 2.5 together with an outline of the usual treatments applied.

The classification of diseases begins with the recognition of consistent patterns in clinical observations. As knowledge of patient response and the underlying biochemistry grows, the multitudes of diseases may be grouped more simply until finally the 'cause' and the particular conditions for each particular disease are established. At present the general state of thyroid regulation has become the initial step in the taxonomy of the 'thyroid' diseases. It is usually followed by a specification of the diseased organ and finally distinguished by the specific pattern of clinical signs. The basic classification structure can be found in Werner and Ingbar (1978). It is important to distinguish between the disease state, the regulatory state and the observation states. Some clinical signs arise directly from the underlying disease state while others appear only because of the failure of regulation. The presence of a thyroid tumour, though of first

importance to overall patient management, is not of interest in studies of regulation except that certain types of tumour are associated with failures of regulation. Before considering individual failures of the components of thyroid regulation, it is necessary to define inadequate regulation.

The final criterion for the success of thyroid hormone regulation is patient well-being as determined by clinical observation in the long and short-term. This implies an idealistic observation of all possible signs on all possible patients and in practice clinical experience is confined to those cases with biochemical or clinical abnormalities associated with thyroid disease. Biochemical signs often precede clinical signs or allow an easier discrimination, but the mere presence of these biochemical states does not justify intervention. The dynamics of the thyroid regulator do not seem of consequence to patient well-being, instead the important variable appears to be the intra-cellular steady-state error in thyroid hormone levels. This means the 'correct' individual steady-state level must be determined together with the sensitivity to any error. The relationship between clinical and biochemical states is difficult to evaluate since the clinical state lags behind biochemical changes and is itself difficult to determine. 'Normal' hormone levels are therefore defined by a population survey or more commonly by a 'well' group without any obvious clinical signs. This population range includes variations which arise from individual conditions, such as age, sex or general health but these are sufficiently small to make the hormone measures good indicators of state. The TSH 'error signal' may also be available in possible hypothyroidism to give an indication of the hypothalamic-pituitary estimation of thyroidal state.

Failures of regulation can be divided into hyperthyroidism (high T3 and possibly T4 levels) and hypothyroidism (low T3 and T4 levels). These conditions are insidious in onset and may naturally remit or relapse over periods of months or years. There are occasional suggestions of generally 'poor' control giving rise to slow oscillations of state but these are very rare. The model described in section 2.5 consists of a number of distinct components which could be responsible for regulatory failure. In practice failure is largely confined to the thyroid and pituitary glands and in particular to the thyroid itself.

The clinical model is therefore not as simple as the regulatory model of figure 2.3. An extended, though still incomplete model, is shown in figure 2.8. The trajectories and divisions of T3, T4, and TSH space seen in figures 2.4 and 2.5 are also simplifications of the observed dynamics under realistic clinical conditions. Thyroiditis for example, may be seen initially with hyperthyroidism as the stored hormone is released from ruptured thyroid cells then with hypothyroidism as the number of active thyroid cells is reduced. Commonly associated with thyroidal hyperfunction are antibodies against the thyroid which mimic the effect of TSH and hence eliminate pituitary control. Viral infection is the factor usually ascribed to thyroiditis though hereditary disposition and excessive ablative therapy to a hypersecreting gland may be other factors. Failures through peripheral resistance or inability to convert or dispose of hormone are almost unknown. The most frequent abnormality arises in plasma protein levels which can normally be compensated for by the pituitary regulation which is sensitive to free hormone fractions. Hyperthyroidism through hypersecretion of the pituitary (adenoma) or hypothalamus is also very rare. Pituitary failures (secondary hypothyroidism) or hypothalamic failures (tertiary hypothyroidism) which degrade regulation are uncommon.

The observations made on these patiens can be divided into biochemical and clinical measures. Figure 2.9 shows the relationship between the underlying state variables and the observations avalable to the physician. Observations marked by an '*' in figure 2.9 were included in the data made avaliable by Mortimer et al (1977) discussed in chapter 7. hormone measures (T4, T3, TSH) have been discussed in section 2.4 and are further considered in chapter 4. Dynamic tests of thyroid or pituitary response were described in sections 2.7 and 2.8 but are not routinely applied to patients since they take some time, require an injection and the analysis of several blood samples. The TRH stimulation test of the pituitary, however, only requires about 60 minutes and three samples and is used in some centres to confirm hyperthyroidism by the suppression of pituitary response. The range of clinical observations is very extensive and an indication of those thought most useful can be seen in figure 2.10 which shows those included in the Crooks-Wayne indices for hyperthyroidism and hypothyroidism (see Wayne ,1954: Crooks et al ,1959: Billewicz et al

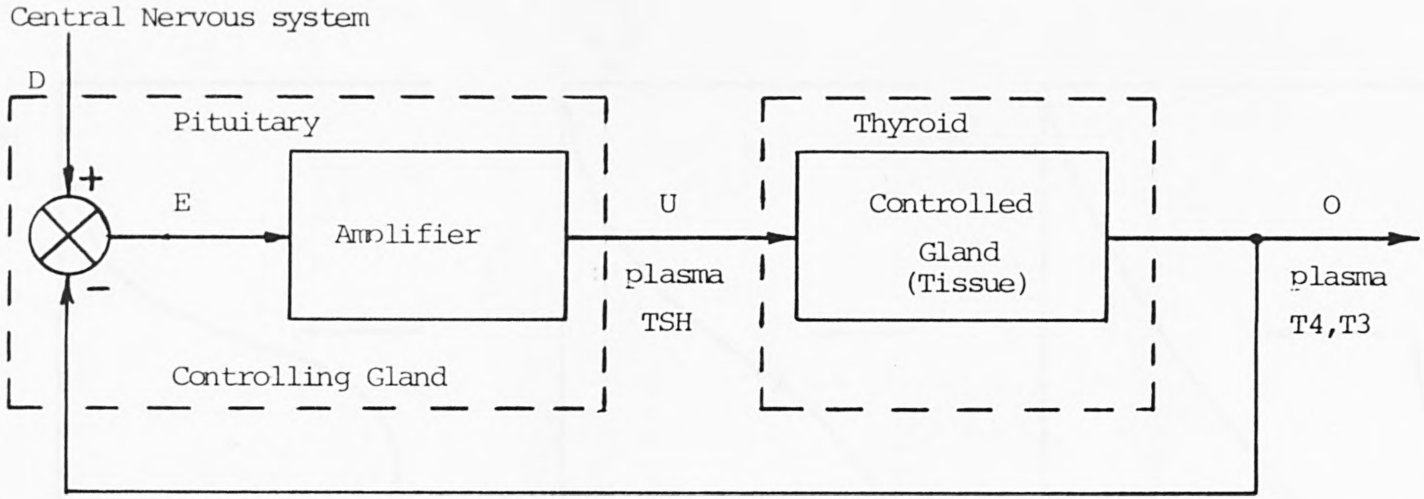
,1969). Except in extremely acute cases of hyperthyroidism (thyroid storm) where efforts are made to 'soak up' plasma hormones, hyperthyroid patients will initially receive suppressive drug therapy. Carbimazole, Methamazole etc block the TSH-like stimulation and reduce thyroidal output. A fall in plasma levels is usually seen within weeks though some, usually well established cases, show resistance to drugs. It is usual practice to adjust dosage to bring the biochemistry and the clinical states back into the normal range. The clinician follows no explicit criteria for therapy selection though it is usual to attempt to normalise state in the minimum time without causing biochemical hypothyroidism and using the smallest dosage possible. It has not been established that drug therapy has any action on the underlying causes of hyperthyroidism.

Response is often straightforward and without problems but occasionally poor control, the appearance of side-effects (particularly skin disorders) with large or prolonged dosages and the need for good compliance suggest ablative therapy. If the patient fails to improve after several years of drug therapy, ablative therapy will probably be considered anyway. Destruction of the gland can be produced by surgery (recommended for younger patients) or by the administration of radioactive iodine (Ra.I.) commonly applied to older patients. A partial thyroidectomy is the aim in either case but as repeated surgery is considered more dangerous than Ra.I. more of the gland is taken to avoid relapse. These ablative therapies increase the risk of hypothyroidism but this is easily treated by hormone replacement and considered preferable to the continued use of antithyroid drugs and the possibility of further symptoms. Hypothyroid patients are invariably treated with orally administed T4. T4 has a half-life of about 7 days so absolute compliance is less important and the effects of prolonged errors less acute. T3 may be given to severe cases as an initial treatment but the shorter half-life requires more frequent doses and, even then, oscillations in plasma levels are observed. As with the antithyroid drugs, the dosage should restore the clinical state as quickly as possible without producing biochemical hyperthyroidism, but the practice is to guess an initial dose and then increase it slowly over months until the clinical signs disappear. In the treatment of both hyper and hypothyroid patients the pituitary can be a useful biochemical indicator, but the lag in clinical response makes the

adjustment of therapy difficult. Hypothyroid patients generally receive a blocking dose of antithyroid drug until biochemical normality is achieved when the physician seeks a maintenance dosage to stabilise the patient. In each case therapy choice is a mixture of experience and trial and error. The physician operates at first much as a 'bang-bang' controller, but experience with a patient tends to improve performance as the physician tries to identify trends as they develop. The uncertain consequences of ablative therapies had led to attempts to estimate the optimum amount of tissue to be removed or Ra.I. to be given in a partial thyroidectomy. Apart from a rough correction according to body weight, this work has had no significant effect upon therapy.

2.12 Conclusions

This chapter has presented the current view of thyroid hormone regulation and used that model as a framework for describing the relevant biochemical and medical data. The regulatory model is used conceptually in diagnosis and treatment but there have been few attempts to apply it directly to patients or to quantify elements for clinical decision-making. At the same time the more detailed metabolic models (DiStefano et al,1975; Saratchandran et al,1976 etc.) have been the subject of extensive efforts to estimate parameters, characterise behaviour and test hypotheses. It would seem appropriate, therefore, to try to apply these models to medical problems. Some of the uncertainties in such models have been described in this chapter but before modelling it is necessary to confirm that the models are acceptable and can be realised within the medical system. The possibility of extending these models is considered in chapter 3, as part of an analysis of the medical system which would use them and the Assay Service which would provide much of the measurement data. The measurement problem is examined extensively in chapter 4.



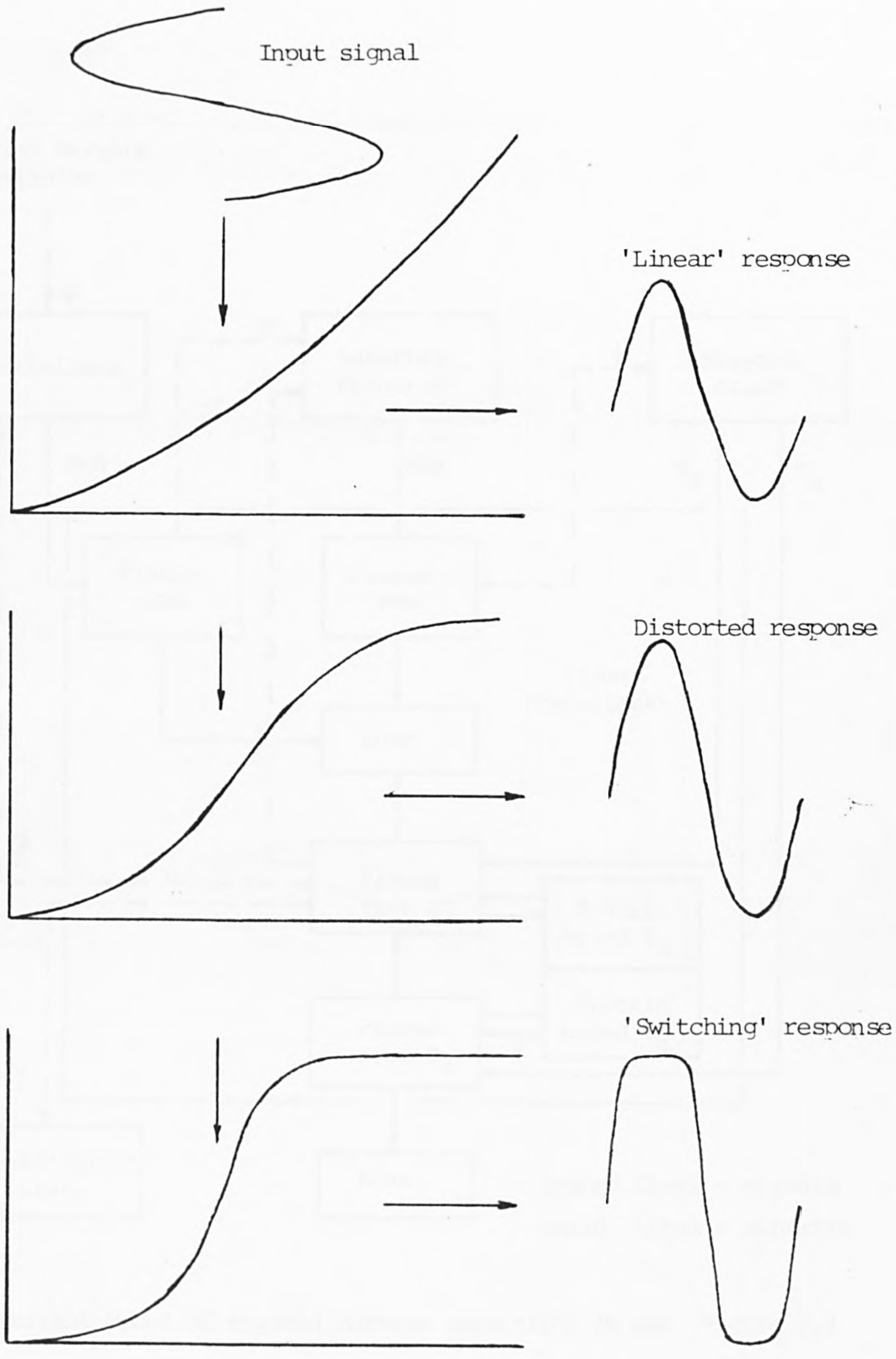
O - Output of regulated system or gland (plasma concentration)

U - Control input, physiological error signal (plasma TSH)

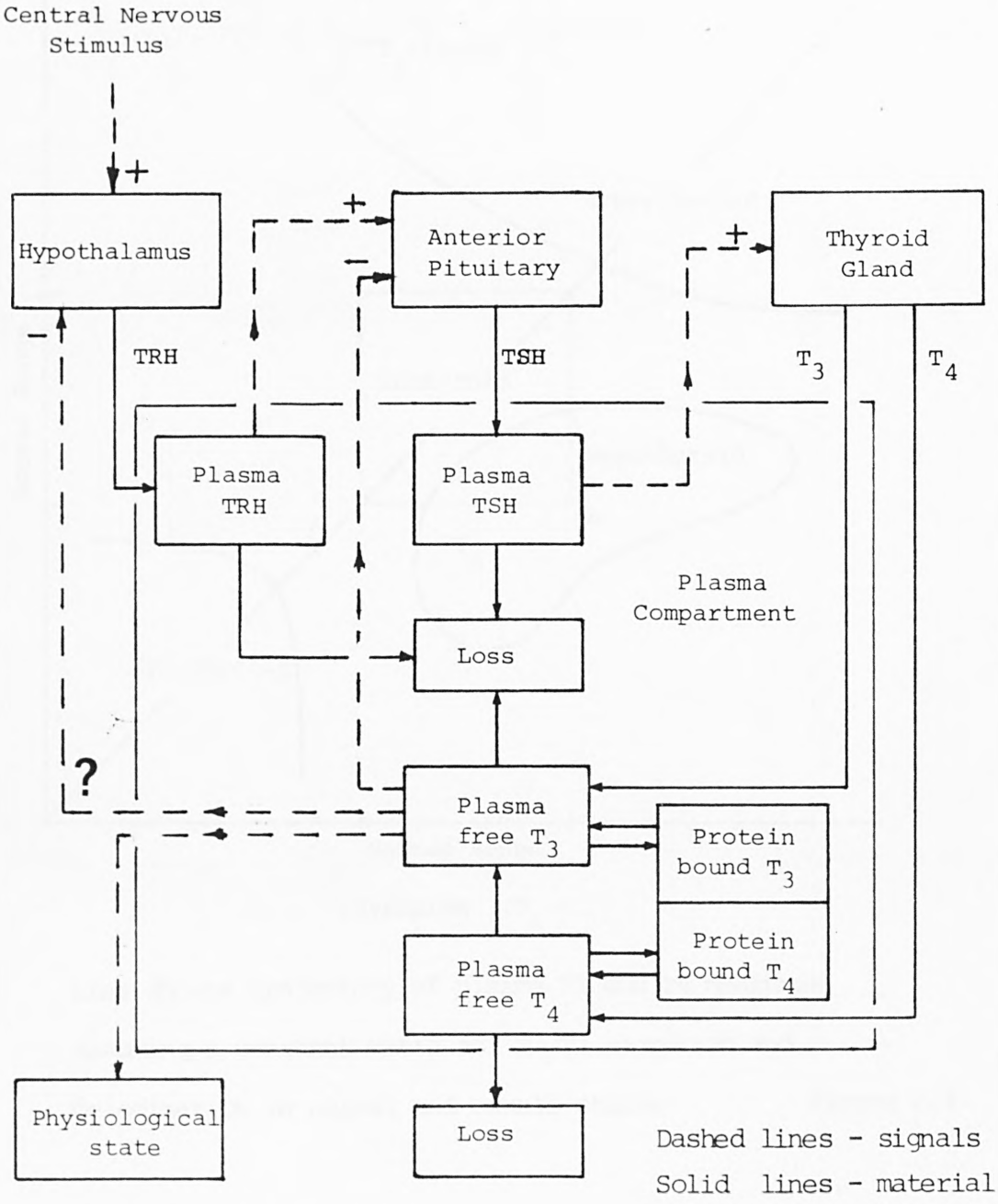
E - Error between desired and observed outut level

D - Desired level of system output (required concentration)

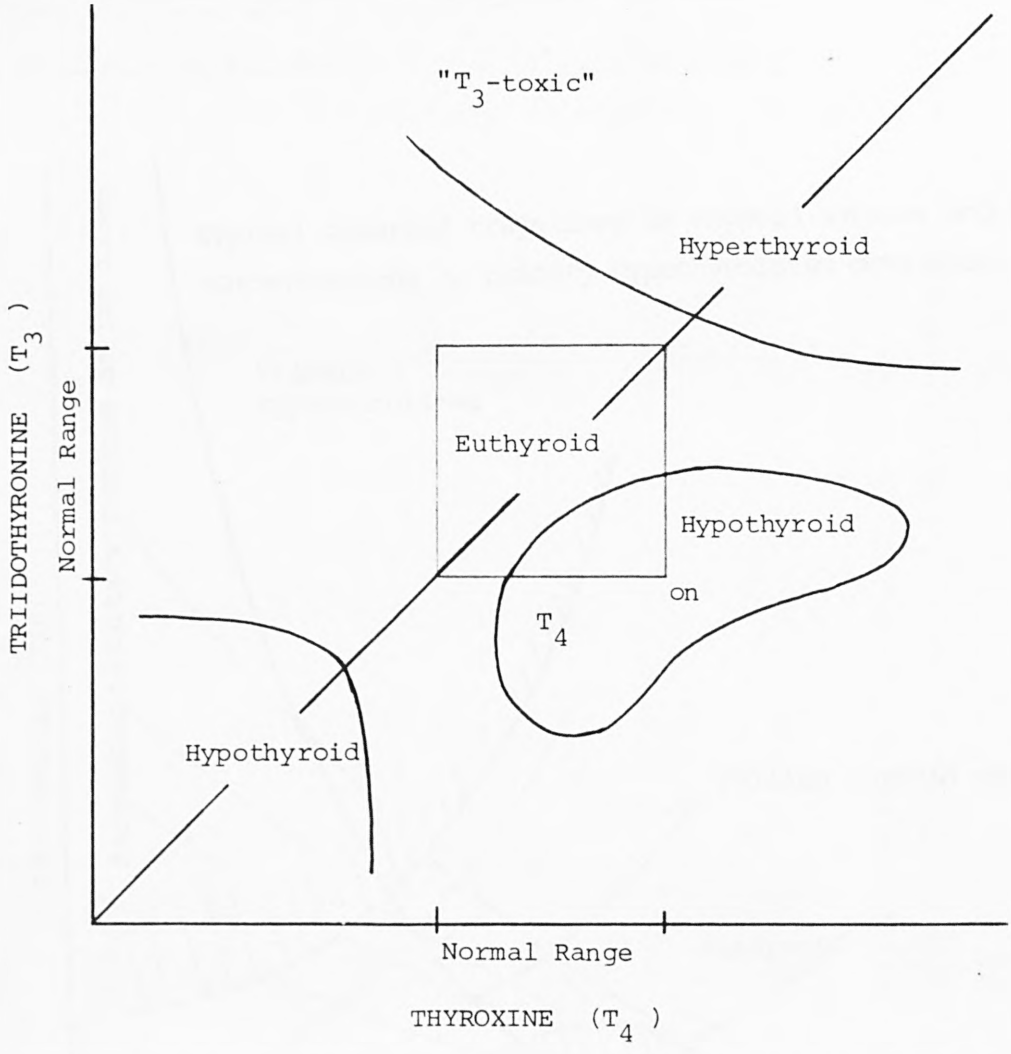
Basic regulatory model of thyroid - pituitary system Figure 2.1



Possible responses from a simple 'chemical' transducer Figure 2.2

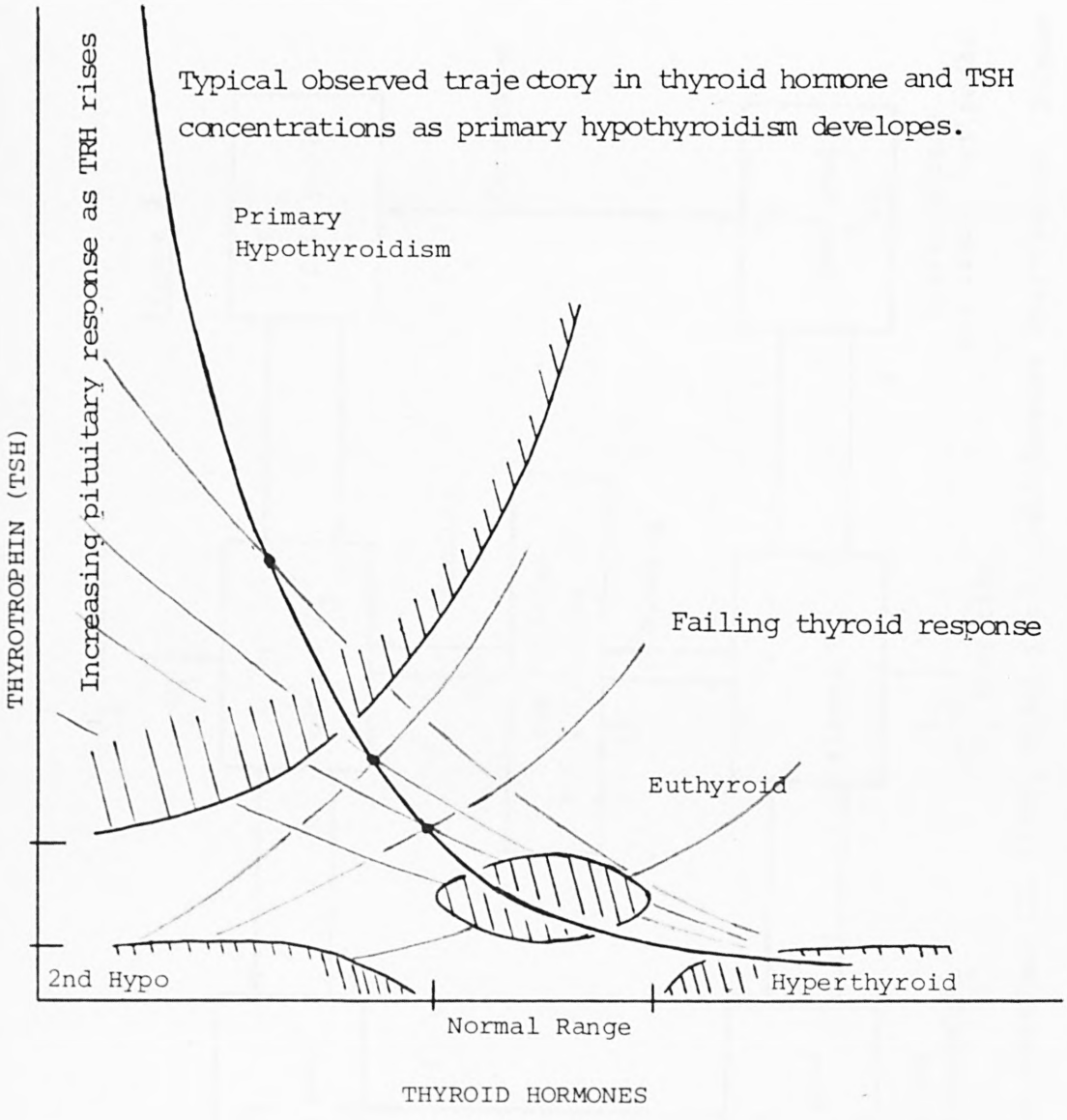


Current Model of thyroid hormone regulation in man Figure 2.3



Line showes trajectory of plasma T3 and T4 measures assuming a constant ratio for T3/T4 secretion and deiodination in normal and unwell states

Figure 2.4



Secondary hypothyroidism (2nd Hypo) arises from a failure of pituitary response. Trajectiory not shown.

Observed thyroid hormone (T3 & T4) vs. TSH in hypothyroidism Fig.2.5

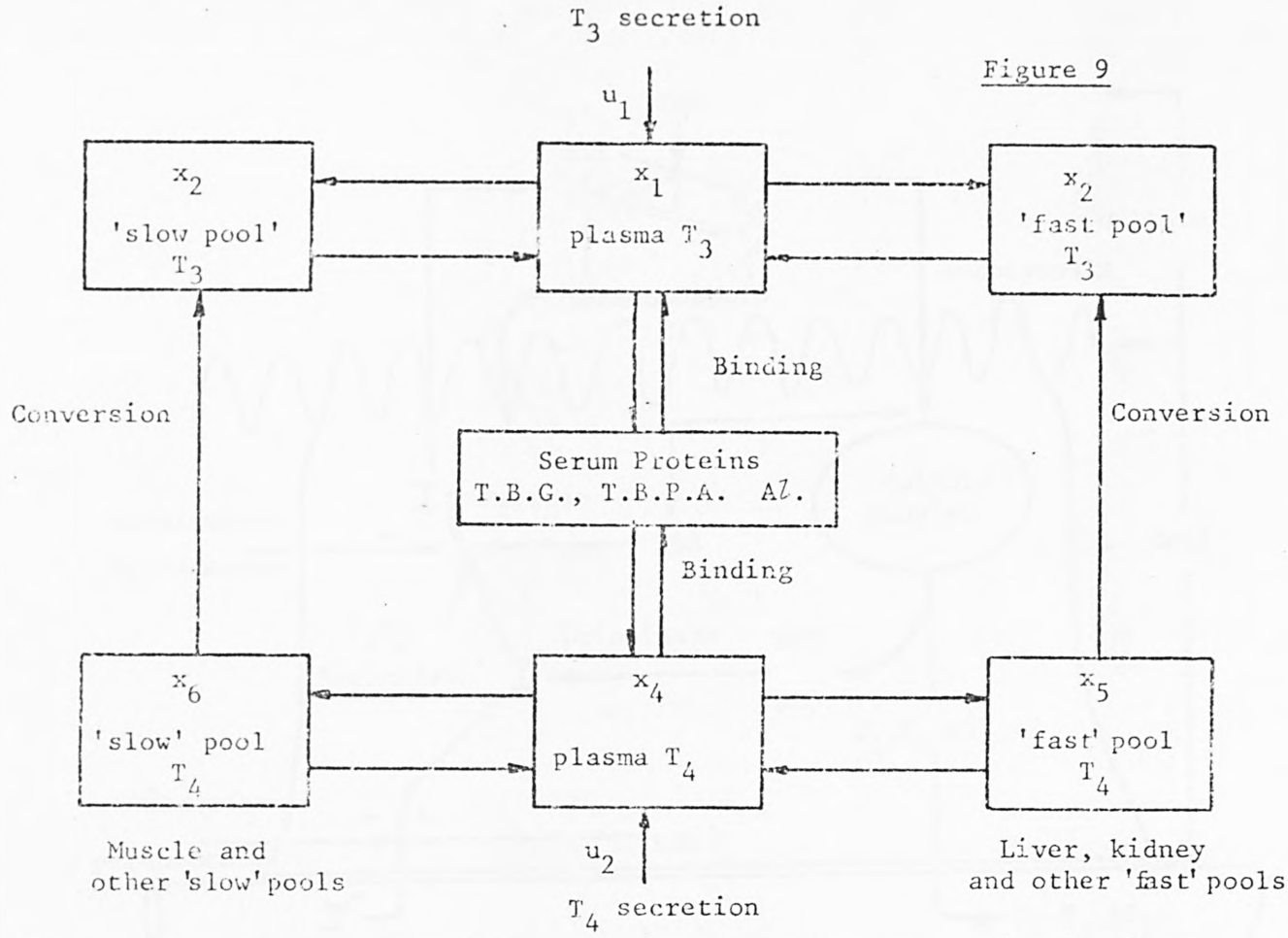
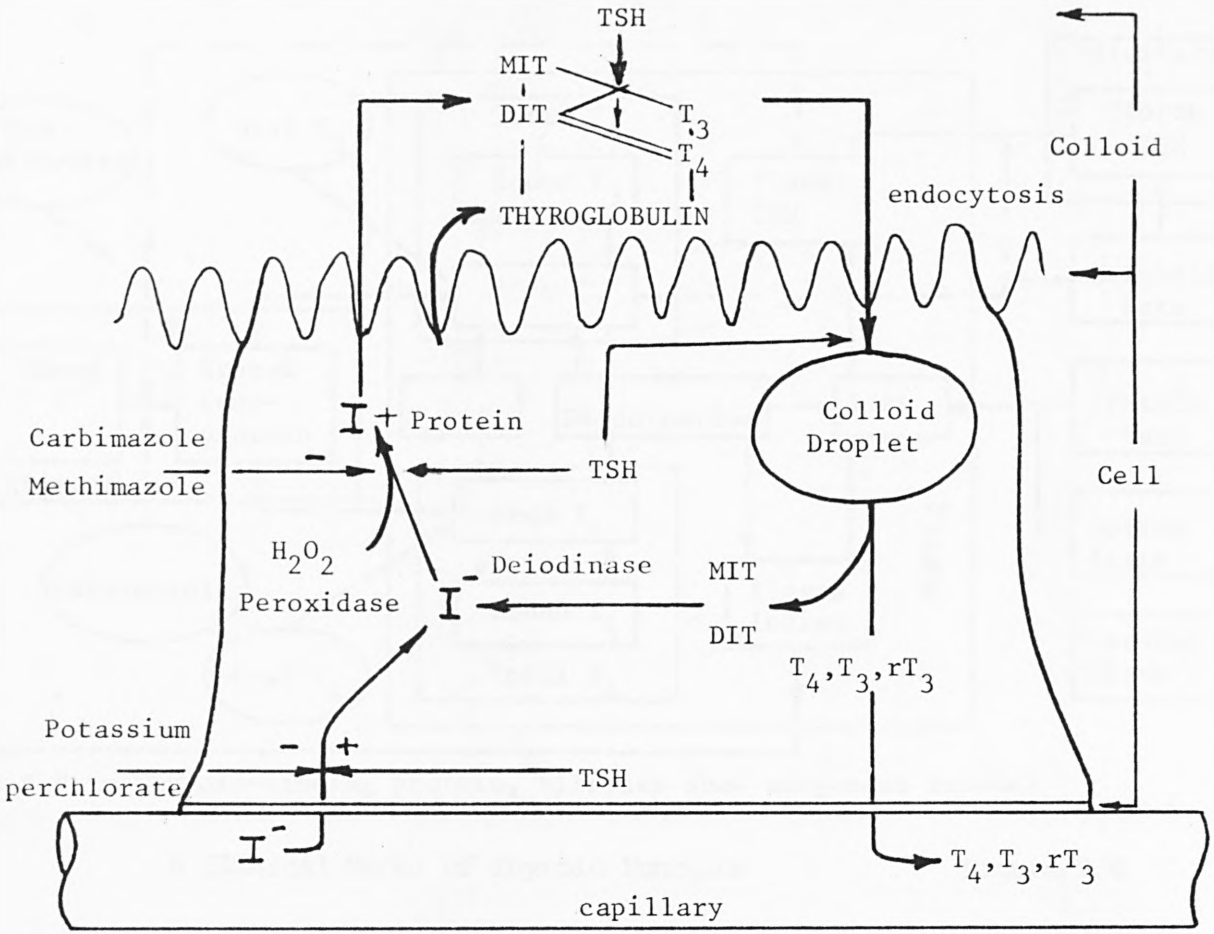


Figure 9

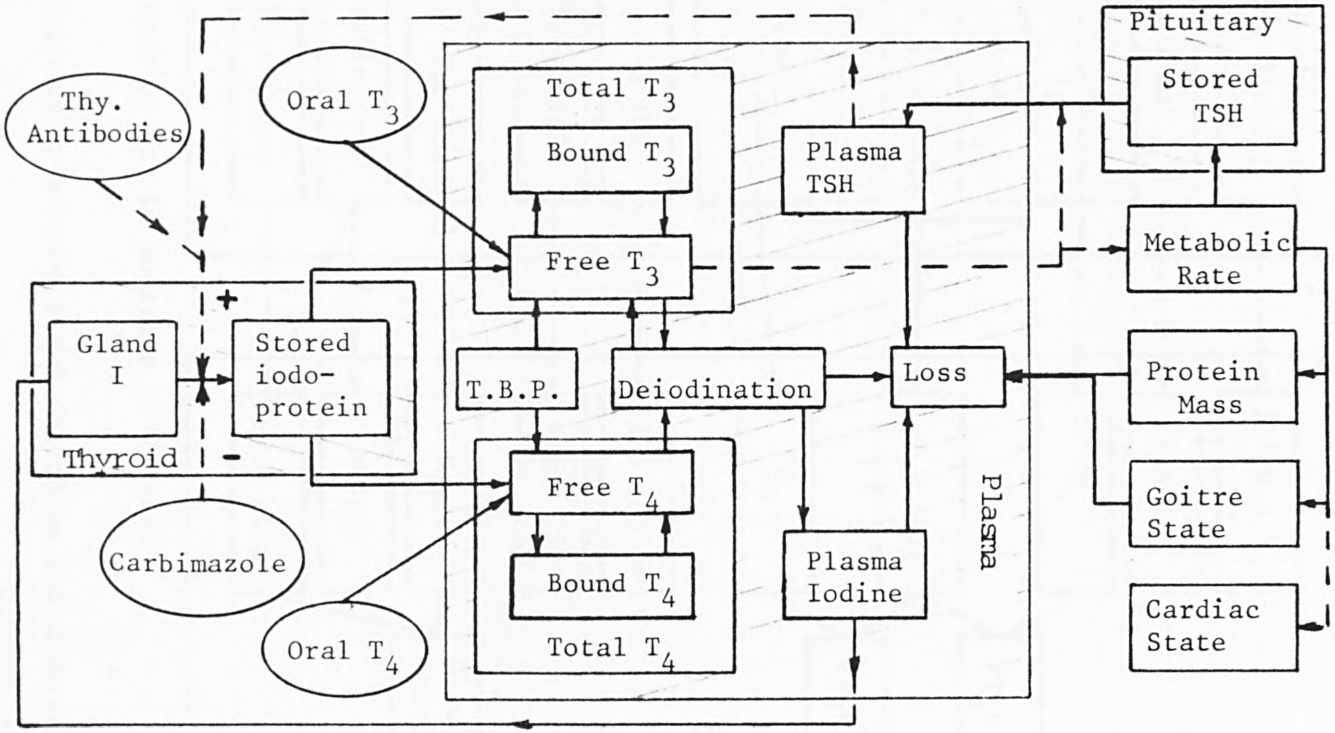
(X_1 to X_6 correspond to state variables see 6.5)

Structure of DiStefano III (1975) Model for Thyroid Hormone Distribution Figure 2.6



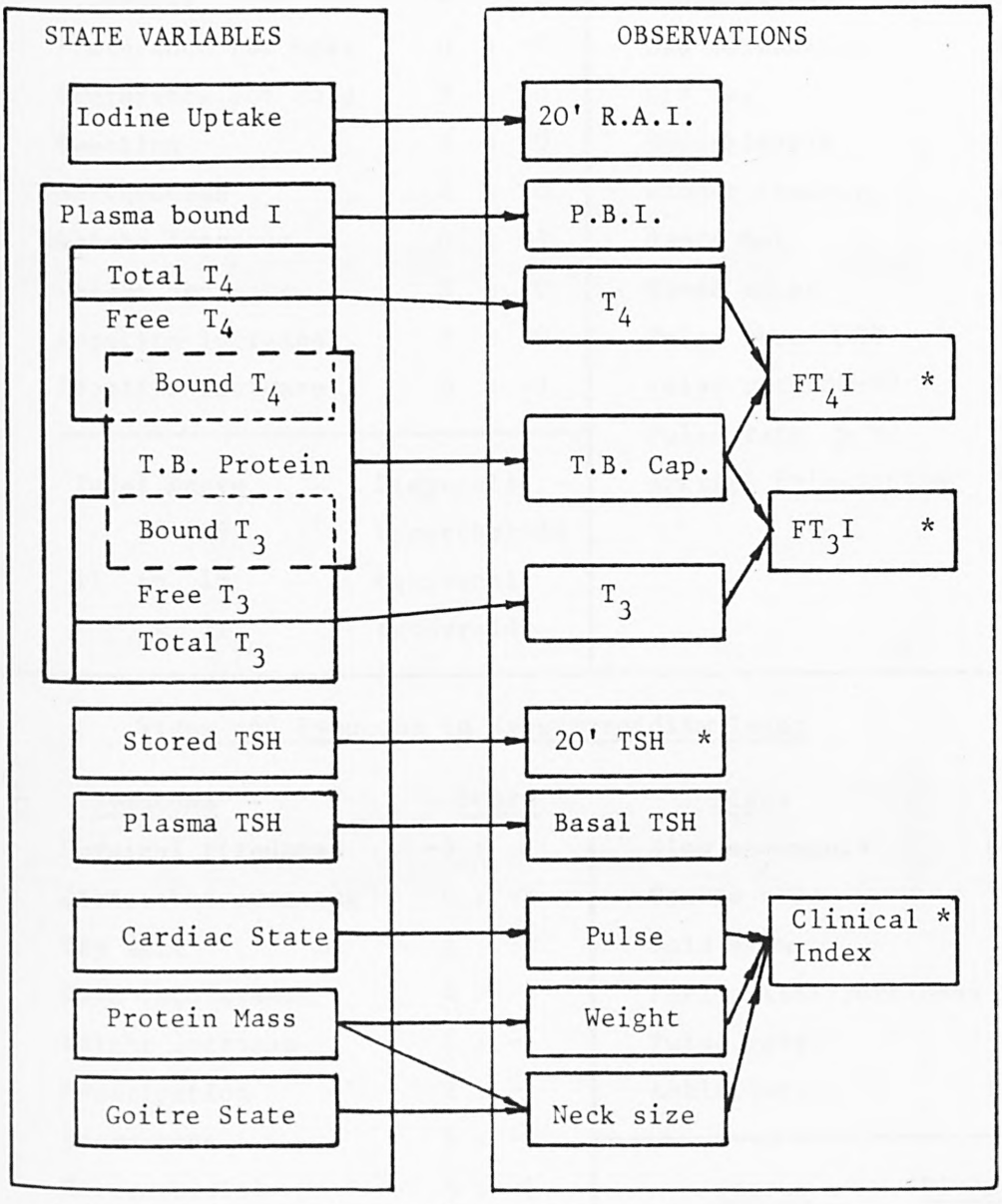
Thyroid Hormone Synthesis and Secretion

Figure 2.7



(T.B.P. - Thyroid-binding protein, Ellipses show exogenous inputs)

A Clinical Model of Thyroid Function Figure 2.8



(*Observation set in Mortimer 1977 data)

Relationship between state variables and observations

Figure 2.9

Signs and Symptoms in Hyperthyroidism Index

Symptoms	Score	Signs	Score
Dyspnoea on effort	1 : 0	Palpable thyroid	3 : -3
Palputations	2 : 0	Thyroid bruit	2 : -3
Tiredness	2 : 0	Exopthalmos	2 : 0
Preference for heat	0 : -5	Lid retraction	2 : 0
Preference for cold	5 : 0	Lid lag	1 : 0
Sweating	3 : 0	Hyperkinesis	4 : -2
Nervousness	2 : 0	Finger tremour	1 : 0
Weight increase	0 : -3	Hands hot	2 : -2
Weight decrease	3 : 0	Hands moist	1 : -1
Appetite increase	3 : 0	Pulse rate < 80	0 : -3
Appetite decrease	0 : -3	Pulse rate 80-90	0 : 0
		Pulse rate > 90	3 : 0
		Artrial fribulation	4 : 0

Total score	Diagnosis
> 19	Hyperthyroid
11 to 19	Equivocal
< 11	Euthyroid

Signs and Symptoms in Hypothyroidism Index

Symptoms	Score	Signs	Score
Physical tiredness	-3 : 1	Slow movements	11 : -3
Diminished sweating	6 : -2	Coarse skin	7 : -7
Dry skin	3 : -6	Cold skin	3 : -2
Cold intolerance	4 : -5	Periorbital puffiness	4 : -4
Weight increase	1 : -1	Pulse rate	4 : -4
Constipation	2 : -1	Ankle jerk	15 : -6
Hoarseness	5 : -6		
Paraesthesiae	5 : -4		
Deafness	2 : 0		

Scores	Diagnosis
< -24	Euthyroid
-24 to 19	Equivocal
> 19	Hypothyroid

Crooks/Wayne Index for hyper and hypothyroidism figure 2.10

CHAPTER 3

A Systems Analysis of Medical Decision-making in Thyroid Disease

3.1 Introduction

The complex processes of diagnosis and medical decision-making have traditionally relied upon the experience and judgement of physicians familar with the accumulated knowledge of medicine and biology. Systems techniques have found an application in the many areas of medical data processing, particularly in the intensive monitoring of acute conditions. In chronic disorders close monitoring is usually less important and the swift, accurate control of the patient less urgent. As a consequence the applications of systems techniques in these areas has not advanced with the same speed. The problem presented by the thyroid assay service therefore provides an opportunity to examine the usefulness of a range of techniques in longer-term patient management. The less immediate needs of these patients means that efficiency,the effective use of limited resources, tends to be of greater importance than maximisation of sensitivity or swiftness of response. This, together with the dispersion of physicians and patients which increase the cost of communication, have limited the application of complex techniques. For patients suspected of thyroid disorders the assay service provides a centre for data processing facilities where a range of expertise is available. It was therefore considered as a possible location for the implementation of medical models which would exploit the neccessary concentration of patient data ,processing power and information handling problems. To establish the goals and the environment in which the assay service operates, a control system model of individual patient management has been proposed . Any general model cannot express the detail and subtlety of the physician-patient relationship but it is felt that for the purposes of discussion of a limited aspect of this relation it forms a satisfactory framework for discussion.

The second half of this chapter develops an analysis of the assay service itself. As with the description of the physician-patient relationship, the emphasis is upon information flow and the model

adopted in this case is that of a multi-access data-processor. The possible improvements and objectives proposed by the control system model are then examined for their implications for the assay service operation. The chapter concludes by proposing a sequence of enhancements to the sevice operation, these conclusions taking the form of a number of proposals. The following chapters are then an attempt to test these proposals and draw conclusions from the results obtained.

3.2 The Initial Problem and Directions of Analysis

The problem presented by the assay service was an exponential growth in the rate of assay requests without, it was considered, an equivalent increase in the output of information useful to physicians. Part of the problem lay in the tendency of physicians to try to avoid the delays involved in having to request further assays if one proved equivocal, by ordering the three routine tests simultaneously. The immediate aim was, therefore, to limit the number of assays on each patient to those necessary to determine patient state adequately.

Three research directions are possible. The first is to seek a single precise measure of the state of thyroid hormone regulation. As seen in chapter 2 the plasma thyrotrophin levels (TSH) correspond to the error signal for the thyroid gland. Thyrotrophin levels provide an amplified version of the thyroid hormone "error" as seen by the individual's pituitary/hypothalamus controller. Unfortunately thyrotrophin assay sensitivity and precision are poor and though hypothyroid levels (high TSH) can be detected, discrimination between euthyroidal and hyperthyroidal levels remains impossible for the simple basal test. Development of the TSH assay continues but the current problem of making best use of the existing tests remains, as will the general problem in medicine of economically exploiting information from a battery of possible tests.

Alternatively the assay service operation could be improved, perhaps largely automated, to reduce assay costs and increase throughput. This does not resolve the real difficulties of the interpretation of results, and usually requires substantial increases in capital and running costs. The approach is popular in the USA where laboratories are profitable but in the U.K. each test is a cost upon a limited financial allocation. There is also a tendency for usage to increase until constraints are met which means that these problems may simply reappear at a higher level of usage.

The final option is to modify assay operation to limit the number of tests performed by reallocating tests in accordance with clinical uncertainty. Work in this direction has already begun and Britton et al (1975) have introduced a simple strategy for new or currently untreated patients. The strategy allocates a secondary test only if the screening test on each patient sample is equivocal. It was therefore decided to try to extend this work to include the whole range of patients for whom these assays are requested. It was soon apparent that a number of developments were possible but no clear idea of the requirements of the physician was available. To determine the objectives and the constraints on these strategy changes, an analysis of the information flows between the physicians and the assay service was undertaken.

3.3 The Medical System

Individual health care is largely carried out within the structure of, and is directed and constrained by, the overall medical system. Beyond and embedded within 'medicine' are the expectations and values of the host society. In health care, as in many large organisations, objectives and constraints tend to be implicit, diffuse and at times contradictory. To proceed it is necessary to propose rather crude models of some of the information processes involved. It must be clear, however, that only a limited part of a particular aspect is being emphasised and the impact of the other components must not be forgotten.

Among other possible motives, the patient expects the physician to identify the cause, or perhaps more realistically the general type of his complaint and recommend a 'restorative' treatment. In this way the physician acts as a controller diagnosing the disorder and selecting a treatment input using some model of the patient in much the same way as the controller of an industrial plant (figure 3.1). In practice a hierarchy of controllers can be envisaged (figure 3.2) rising from the cellular and physiological regulators through consciousness and peer group opinion to the detailed knowledge of the specialist. As the physician's knowledge grows he tries to extend his role to cover wider aspects of health-care. This can lead to a conflict as the expansion of professional function draws in more and more medical problems and produces an increasing number of patients suspected of increasingly "trivial" disorders. To deal with this, a commensurate increase in controller capacity is required either by the high-level medical staff or by a lower level filtering, performed through the patient's own

knowledge of health and illness. Similar problems of sensitivity and selectivity arise when screening programmes are undertaken.

While it is clearly difficult to establish a comprehensive list of objectives or to discuss in any detail the whole system, a number of general aims can be proposed. The overall medical system seeks to achieve a fair and effective distribution of resources among a community. This might be summarised as a minimisation of an overall weighted patient risk per unit cost. In practice weighting of relative benefits and risks is impossible so for subsystems of interest we may consider that the overall objectives have established cost limits but within them allow maximisation of patient "benefit". The perceived needs of the individual patient naturally tends to conflict with these overall aims and the physician has to resolve these differences for each patient. Each auxiliary service, including the physician himself, can be considered a subsystem which derives its objectives in part from the objectives and needs of the individual , partly from general health care, and finally the aims of involved personnel. The aims of the personnel are not considered explicitly here but ease of operation, job satisfaction, and the like must be included if any changes in procedures are envisaged. In the next section the information flows within individual patient health care are examined.

3.4 Individual Health Care as a Control System

The control system analogue proposed earlier can be expanded and used as a framework for further discussion. It is not suggested that all aspects of the physician-patient relationship can be usefully expressed or included in this format. It is, however, a vehicle for describing the relevant aspects of information handling which would be expected to form part of the interaction. Figure 3.3 shows the structure of the control system model which will be discussed here.

3.5 The Patient and Medical Record

It would be generally considered unwise to divorce the patient from his environment but the patient is often the source for such "background" information so the environment may be considered part of his attributes. The observations made by the physician from the potentially infinite set of attributes reflect his prior expectations and models of the patient. These can be taken as being largely intrinsic to the physician. It is important that these models are sufficiently detailed and accurate. They arise and are modified in

three ways: medical knowledge aquired through training or reading, long-term experience with different "types" of patients and disorders, and finally by learning the characteristics of individual patients. The flow of information back up this chain has been the traditional route for the growth of formal medical knowledge. It relies, however, upon complete and accurate medical records which can easily be accessed or at least upon the opportunity to draw together these data. The medical record can be considered as a part of the observable patient attributes but are often poorly organised and data on individuals or groups are often difficult to retrieve. Cures have been proposed (ie. problem-orientated records, computer based records) but are generally limited by time and motivation or clerical effort and processing difficulties. Generally the amount of information, particularly quantitative, which can be drawn from the existing medical record is restricted by the effort of recording, retrieval and presentation. In acute situations, the more intensive care and greater facilities, mean that many more short-term measures are recorded and much more complex processing and examination of data is routine.

Only aspects of information flow considered relevant have been mentioned here. The mechanics and management of record keeping, the clinic itself the associated nursing services have major effects upon the amount and success of data handling. As these subsystems are largely independent of assay service operation their analysis will not be attempted. It is clear, therefore, that any system changes that affect these components must be tested in practice before being recommended for implementation.

3.6 Sensors

Observation of the patient may be considered as a complex filtering of patient attributes which yields features useful for diagnosis and decision-making. The distinction between observation and diagnosis corresponds to the distinction made in pattern-recognition between feature selection and classification. As in pattern-recognition the division is largely a pragmatic one. Diagnosis could not cope with all possible 'raw' measures or statements while a sufficiently sophisticated feature extraction would make diagnosis trivial. The observation process corresponds to part of the complete model used by the physician to describe the patient, his disorder and to guide his investigation. Often complex processing is invoked to yield an observation such as

"mild upper arm skin rash" which might alone be a complete symptomatic diagnosis. Observation is made at some cost in time and, possibly, risk. This leads to the problem of off-setting these observation costs against the cost of instigating treatment when uncertain of the outcome. Two major strands have developed in work in this area. Firstly the evaluation of the actual costs and/or utility associated with any action and then secondly the developement of the algorithms for combining and comparing the probability of incurring these costs. The real problems lie in the quantification of costs and values and the assumptions which must be made when combining such costs. In practice unless an acceptable procedure for including these complex value-laden criteria is available, efforts at quantification and production of algorithms which maximise a utility are of little real use. At the same time some attempt at an appraisal of benefit is necessary, even if largely qualitative or exploratory. Cost, as distinct from 'benefit', is easier to determine and it is often possible to substitute and operationalise an implied benefit like information. In these cases a simple comparison of costs for a given infomation output may be satisfactory. The information can then be valued by its subsequent effect on therapy selection.

The Thyroid Assay Service can be introduced at this point since it can be viewed as a sensor instructed by the physician to measure certain biochemical variables and give a result outside the consultation period. Apart from the costs of the actual measures, this means the result is not immediately available for decision-making and at some time after the consultation (usually about a week) the phycision must examine the patient's medical record and the assay result.The provisional therapy chosen during the consultation is reviewed and any change in management requires a letter to the patient. This means that irrespective of the laboratory costs there is a significant clerical cost in requesting an assay at all. Against this the physician often feels the need to confirm his clinical judgement and to reassure the patient.

The assay service retains any residual plasma after the assay so an uncertain result does not normally require a further blood sample, but the delay and clerical effort of sending out a request are repeated. As a result the physician, who may not be certain as to the particular assay required anyway, is inclined to request all the routine thyroid assays simultaneously. This increases the sensitivity for the detection

of thyroid disorders but reduces the selectivity of discrimination by producing more false positive results. These in turn mean further assays or the use of more complex tests. Conversely the cost to the assay serrvice would be reduced by sequential testing but this would conflict with the objectives of the physician who seeks to maximise a benefit, seen as information for diagnostic resolution, by ordering the tests in parallel. simultaneously . To limit the clerical workload of the assay service, the physician is required to supply an individual request form for each assay but the number of requests continued to rise.

A way to largely resolve this conflict would be for the recording of clinical state and initial test results. This would produce an operation which, in terms of cost, delay and information provided, fell between the parallel and the sequential types. The clinical and biochemical information could be weighted to minimise the effect of these cost-benefits. In requesting a test, it is already usual for the physician to supply some data on his assesment of the clinical condition and drug status of the patient. These data are, however, generally poor in reliability and precision. To increase the content implies an increase in costs. Clearly it is impracticable to attempt a complete cost-benefit analysis and furthermore the response of the medical system is liable to depend upon a range of pressures. If the assay service is to assist in test selection then this expansion implies the inclusion of parts of the diagnostic and descion-making roles at least in the objectives set for selection. Apart from professional reluctance, the data flows required will limit the extent of this expansion. These aspects of the overall-model are considered next.

We have suggested that medical assessment can be conveniently divided into observation and classification or diagnosis. The subsequent decision-making applies the diagnostic statements to a set of values and objectives to select further action. Models have already been implied in the observation process which filter those attributes and relations considered to be of importance in the patient, and models are further employed in diagnosis and decision-making. The diagnostic model is usually a construction which relates current symptoms to their subsequent pathology and the concepts thought to underly the disease to a general taxonomy. It includes a number of "rules of thumb" often partly drawn from the experience of particular physicians for the

identification of disorders even if masked or compounded. The model may produce a simple estimate of current state or a prediction of likely response to therapy. Model form depends upon the particular concept of disease used. Often a disease is registered only as the coincidence of certain signs with perhaps knowledge of the final state or affected organ reflected in the name. In rare cases the aetiology and progress of the underlying disorder may be well established and a complex model relating biochemistry to clinical state is availible. Unfortunately much medical or biochemical knowledge, though of explanatory or descriptive power, may not be useful in clinical practice where simpler structures or those giving more emphasis to important clinical features are applied.

Attempts to analyse the mental processes or the detailed procedures involved in diagnosis are uncommon. Rather studies have assumed some structure to identify features and to indicate how relations between them define or estimate the likelihoods of the disease classes considered (Logical relations,Bayes,Maximum Likelihood etc). Beneken et al (1979) suggest that these various attempts to predict disease state can be divided into three types: Indices based upon current measures, identification of "trends" in time-series data and "trend prediction" which is a prognostic statement based upon prior information and the current measures. The fist two types are usually used to estimate the existing patient state while trend prediction attempts to extrapolate some variable through time. This, though a useful summary of types is essentially a progression of increasingly complex patient models including at each stage a greater number of measures, more prior knowledge and more predictive precision. At the simplest level a single measurement vector is used to discriminate between classes which have been defined by several distinct outcomes or behaviours. This is the pattern-recognition approach where, despite an apparent lack of explicit model structure, a large number of assumptions about the observations and their interrelationships are required to make the problem tractable. As noted earlier the pattern-recognition model can be divided into feature extraction and classification (figure 3.4). Feature selection is the isolation of important features from the raw data which are suitable for the particular classification technique employed and is usually unique to each problem. Classification is a more general aspect, probably statistically based, which relies upon certain

assumptions about the features presented - such as homogeneous classes in feature space. The pattern recognition approach is not limited to a simple index or estimation of state, but, as predictions are extended the model used to describe the patient's disorder grows more complex, as the range of measurement variables or the domain of prediction is expanded or made more detailed. Feature selection can be extended to give as a single feature an indication of the presence of a significant trend in time-series data, while prediction might grow from a decision between two possible states, to estimating a continuous trajectory through state space. To make increasingly detailed predictions, model complexity must be correspondingly increased either through prior knowledge or a considerable increase in local data used to identify the model. A trade-off exists therefore for any structure between identifying inputs from a priori and locally available data. In the statistical classifier, the combination of a large feature set and limited data or prior knowledge can easily make predictions unreliable through the familiar "curse of dimensionality". The quality of the assumptions used initially to establish the model is particularly important if extrapolation beyond the range of the training data is envisaged. Frequently these assumptions are included by default rather than on the basis of substantive evidence. This is especially common with statistical classifiers which are often favoured for their apparent lack of prior structural information.

Underlying these models is a corresponding range of concepts of disease. A "cybernetic" notion of disease would emphasise a breakdown of internal regulation caused by inputs from an external agent or an internal component fault. Generally satisfactory "causes" cannot be advanced and disease is regarded as descriptive and predictive classification of observation-disease concepts serving as a "vehicle" for clinical experience. This resembles the pattern-recognition problem in which the notion of "similar" images is quantified by some algorithm and it seems plausible that established diseases would correspond to distict patterns or clusters in a feature space chosen because of its expected relevence to that disorder. In cluster analysis for example, observations upon individuals are represented as points in feature space. The similarity between observations on different patients can then be quantified as distances in this feature space with particular conditions or disease states appearing as distinct clusters. Despite

the apparent directness of this method and lack of explicit prior structural knowledge, few workers appear to have obtained the expected clusterings. Glueck et al (1969), for example, found little relation in psychiatric patients between the vague clusters generated and the expected diseases. Other authors have shown comparatively poor relationships between the known clinical entities and measured groups. The mathematical opaqueness of these al gorthms and the suspicion that non-representative patients or measures were used has led to a decline of interest in this area. It would seem, however, surprising and of some consequence that a rational examination of "relevant" measures on a real patient sample failed to identify the textbook disorders.

A number of factors can be suggested. Poor precision in the clinical or biochemical measures used could inject sufficient noise to obscure classes. Insufficient medical knowledge included in the feature extraction model can lead to a number of problems. Glueck et al (1969) with the same data moved from a clustering to a discriminant procedure which required information on class membership and relative frequencies, to achieve a 90% success rate in the discrimination . Simple temporal changes can produce not only multiple clusters for a single disease type but tracking effects between these clusters. Indeed in the feature space considered it may simply be incorrect to consider a single class for a disorder. Many conditions are progressive, at lease at onset, but may never show a full pathology. It may be that the disorders would be distingushed by complex features which included some of these tempporal factors or invoked a "fuzzy" definition. A fuzzy definition would however not explicitly include the progressive transition between classes and in any case a complex discriminator is implied.

The clustering definition of disease discussed here can usually be derived exactly from the logical discription of the disorder available in medical textbooks. Clustering techniques give a quantification of this definition in a particular location and may be useful, particularly as disorders are at times redefined as new or more detailed measures become available. Spitzer et al (1968) developed a logical decision tree for the classification of psychiatric patients built explicitly upon detailed clinical considerations at each decision point for both hypothetical "ideal" patients and real cases. The final decision tree was complex, included re-entrant paths and the simultaneous evaluation at each of the 57 decision points of up to twelve features, out of a

possible 90. Clearly this programme includes a complex model of the disorders and the relationships observed between features that are derived from general medical experience. Testing against statistical classifiers (Bayesian, assuming linearly independent features and a linear discriminator) showed that the statistical routines performed better on their training sets, approximately the same on a test set from the same population and worse on a test set drawn from a new patient population. Workers have justified discriminant techniques in diagnosis as a way of isolating an optimal subset of features for diagnosis. Bouckaert (1974) showed a particular subset of features to be optimal in the discrimination of Goitre conditions. This "optimum" is, however, not uncommon in many pattern recognition problems where a relatively large feature set is used with a restricted data base. Duda and Hart (1973) explain that, for a given classifier and training set, such an optimum is to be expected. It also explains why a simple linear classifier often gives the most reliable results. Higher level classifiers more quickly become under-determined as the classifier "learns" the particular characteristics of the training data by the production of a complex decision surface bearing little relation to the underlying distributions. The classifier then performs poorly upon new data but this may not be observed because workers often omitted testing the confidence of their classifier parameter estimates.

These critiscisms do not mean that statistical classifiers do not have a clinical role. It does imply that two general conditions must be satisfied. First they should have some well defined objectives from specific problems in health care which are well-posed and secondly estimates of the confidence of the parameters obtained should be made. For "well-posed" we require a clear problem in the discrimination of distinct disorders in a defined feature space itself derived from some clear model of the relevant clinical attributes.

The literature on diagnostic algorithms generally is extensive and has been recently reviewed by Wardle et al (1978). The authors differentiate between three types of diagnostic model depending upon whether data are examined simultaneously (I), sequentially (II) and whether the cost or utility of each measure is considered (III). Wardle claims that the sequential models are sucessful in replicating the physician's behaviour but agrees that the difficulties of establishing costs and utilities have largely been avoided. In fact a physician is

likely to examine groups of signs simultaneously and decide whether to continue seeking information. The amount of data and the type depend not only upon the disease but the individual patient and condition. Other criticisms made by Wardle include the lack of comparison with results achieved by physicians alone or by using other techniques working under similar conditions. Indeed Wardle notes that the methodology and conditions are often poorly defined. Bayes and various forms of linear discriminant analysis have been occasionally compared with other techniques, surprisingly without consistent improvements being observed. A form of hierarchical clustering using the nearest nerghbour rule can, for example, generate spanning trees of great complexity and similarity functions sensitive to local conditions can distinguish between tightly interwoven clusters. Unfortunately the difficulty with medical data is mainly centred about the uncertainty of the measures available. Worse still, the degree or type of uncertainty with any particular measure may itself be an unknown. Measurement noise is quite sufficient to drown the precise delineation of observation space, which these algorithms assume. Results with higher order classifiers are usually only better on the original training set, an artifact of the experimental process well known in statistics generally, but only recently are attempts being made to evaluate the confidence of parameter identification in more complex bio-models. (Carson et al 1982)

To summarise, operational problems arising in the application of classification techniques to medical decision-making are associated with the indeterminacy of sparsely structured models with noisy measurements. This approach can be applied to thyroid health care but carries with it the following requirements:

(1) A realistically limited and defined problem.

(2) 'Relatively' accurate and precise measures often difficult for clinical data.

(3) A substantial and preferably continually updated data base drawn from the population of interest.

To propose a system which can obtain these conditions at realistic costs and to show that the system produces diagnostic benefit is the overall aim of this chapter and the pilot study described in chapter 4. Before consideration of the data-handling system, another avenue remains to be considered. The model used may be extended by the addition of

further a priori medical knowledge of patient and medical actions. This is readily obtained by extending the control analogy directly to the management of the individual patient.

3.7 Control Models Applied to Health Care

In this section the attempts made to apply more complex models to the management of patient condition will be considered. The control analogue has been proposed by a number of authors, in some cases stressing the need for an adequate patient model and satisfactory control criteria, but few have given real applications or details of implementation for individual patients. Since many disorders are inadequately understood, involve subtle perhaps conflicting criteria or difficulties in measurement, exceptions are largely confined to problems where measurement involves high data rates such as E.C.G. analysis or X-ray image enhancement. Again the measurement problem reappears limiting the structural knowledge available on the relationships between clinical variables. Model formulation is therefore limited with consequent effects upon the probability of identification of individual patient characteristics, so that "optimal" therapy can be selected. The complex metabolic models available in some areas, such as thyroid hormone regulation, must be largely excluded. They are mainly directed towards the description of short-term behaviour in the normal or non-physiological conditions and are usually indeterminate given normal clinical measures. The possibility remains of using less complex models based upon clinical measures which may be able to show benefits in the selection of therapy and in the choice of a maintenance strategy. A number of approaches will be discussed below, but it can be seen at once that again the need for reliable measurement must be satisfied to allow model formulation, identification and control. Measurement systems are prerequisite for the application of any further analytic or predictive processes.

Given reliable clinical and biochemical data, appropriate models can be developed. Behaviour over time, such as the response to therapy, can then define the classes of patient to be identified from parameter estimates. The problem can be restated as one of stochastic control and the problems of the classification approach reappear in terms of state observability, controllability, and the reliability of parameter, and hence, state estimates. The choice of criteria to judge the operation of health-care has already been discussed and the physician translates

"patient benefit" into desired changes in observed patient state. An example appears in Mak et al (1980) where benefit has been equated with two alternative criteria: minimum time to acheive normal thyroid hormone levels and minimum thyroxine dosage. In this case patient condition is defined on the basis of the biochemical state while it is the clinical state that is of immediate importance to the patient. This paper (Mak et al 1980) is a theoretical study using the model of thyroid hormone distribution developed by DiStefano et al (1975) to estimate optimal replacement dosages of thyroxine for hypothyroid patients and show clearly the problems of employing such complex multi-compartmental models in clinical situations. The model parameters were partially identified for three normal individuals (DiStefano et al, 1975) by small perturbation studies requiring a large set of samples to be taken over a period of minutes to hours. This is impracticable and unnecessary in routine clinical practice where a few measures are made over weeks while therapy is adjusted by trial and error. It remains to be shown that the three normal individuals are representative of any population of hypothyroid patients, that there are no long-term disturbances in abnormal thyroid function, that residual regulatory effects are negligible and that any significant benefits or savings will follow the therapy chosen.

A different formulation is proposed by Gheorghe et al (1977) in which a partly observed semi-Markov model is used to link the fault (underlying disease) and changes in patient state, by cause-effect models which are related through the observations made. The relationship between the "cause" and the resulting physiological state is obtained by a logical multiplication of the associated probabilities. Again the difficulty in application lies in the lack of observations which can be used to evaluate the probabilities which define the model parameters. This form also lends itself best to discrete states and is less appropriate for the progressive failures of function seen in many cases of thyroid disease.

Having considered a number of techniques, it becomes clear that the quality and extent of biochemical and clinical data will be a major factor in the development of successful models of any complexity, particularly if they are to find a routine medical application. It is therefore necessary to examine the information handling processes currently used and to consider feasible modifications if increased

amounts and quality of patient data are required.

3.8 Information Handling by a Thyroid Radioimmunoassay Service

In this section the role and operation of the thyroid assay service is examined. Attention is concentrated upon its present role as part of the physician's "sensors" and upon the data handling required rather than the procedures involved in particular assays. Assay optimisation can be considered to be a related but distinct problem at a lower level with criteria taken from higher objectives. The assay service is a facility available to assist individual health care and shares the physical and financial constraints of other hospital facilities. These, together with constraints particular to the service and the requirements of individual health care, establish the local objectives of the service. The general objective of minimising patient "abnormality" and discomfort can be interpreted by the assay service as a requirement for maximum information rate. The data returned by the service are only useful if they can have an effect upon medical decision- making. Maximum data rates do not neccessarily mean maximum information as, if excessive, they may introduce noise as well as increasing costs.

It is possible to consider a service which tailored its output to the exact requirements of each physician and patient, but the clinical data need would be costly to input and process. The existing system operates at a stable point among these competing factors and any changes proposed must show the physician either a reduction in effort or a trade-off of increased information for effort. To do otherwise would reduce the overall effectiveness. The load seen by the physician now is mainly clerical, filling-in of the request forms , and the delays in response. To minimise their own clerical effort the service has evolved with little interpretive function. The physician brings together patient data and the raw biochemical data to be interpreted on the basis of experience and medical knowledge. This reflects the central role of the physician in collating data and in decision-making on the individual patient. Any changes should assist this operation without imposing excessive clerical loads, duplication of the physician's role or obscuring the basic measures made available.

3.9 The Assay Service System

Figure 3.5 shows the steps that each request passes through from its appearence with the blood sample to the return of the request form with the result on its reverse side to be stuck into the medical record.

These steps may be re-interpreted as part of a data processing system as shown in figures 3.6, 3.7 and 3.8.

The assay service is limited here to the routine in vitro tests provided by the Department of Nuclear Medicine at the Middlesex Hospital. It is part of the Department's wider research and testing function it could be argued that only sample reception is employed solely to meet the needs of the assay service. A service commitment does, however, form a substantial part of the duties of many members of the staff. Users of the service range from hospital consultants receiving perhaps tens of results per week to "outside" physicians receiving occasional results. To use the service the physician must supply a standard request form identifying himself, the patient, the (single) assay required and any clinical details thought relevant together with a blood sample. Request and sample appear, usually simultaneously, as part of an uncertain number of jobs to be sequenced and sorted by reception. Here, the occassionally crumpled and stained forms are examined and the relevant test selected. The blood samples are spun to seperate the plasma which is transferred to a small assay tube. A common identifying number is applied to tube and form, then tubes for the same assay are batched and stored in a freezer. At the same time work sheets are drawn up for each assay identification, details of each request are included and the sheets used for each "assay" performed in batches at intervals by technicians. As only a small amount of plasma is used by the assay, sufficient usually remains for repeated or further measures. The residual plasma is stored and may eventually be included in a plasma pool used for "standards". Assay results are derived from raw counting data by computer analysis but must be transfered to the work sheets manually. The completed work sheets and the computer generated assay error report are checked by a supervisor who confirms the results as they are entered on the request forms for return. The work sheets are retained to provide a duplicate record of the assay. The work sheets are filed and are available in case of enquiries about lost requests or the production of statistics on assay usage or quality. While figure 3.5 shows the basic sequence of these operations, figure 3.8 emphasises the importance of reception in controlling data flow. Through reception flows data to and from the user, converting his problem into a form suitable for processing and then interpreting the results. This is clearly the location for changes

involving increased data capture or interpreative effort. Already at this point clinical data are abstracted from the requests to produce the (typed) worksheets, while, after the assay, the results must be copied from the print-out, evaluated and written on to the original forms. The introduction of a computer terminal to bring this file handling "on-line" would appear to be a logical extension of the existing computing facilities. The aim would not be to "automate" the tasks of reception but to allow the possible advantages of greater processing power to be reflected back to the user without imposing an excessive clerical load upon either sevice or user. This is an important factor since the clerical effort needed to capture data is often the practical limitation upon computer usage.

Figure 3.8 breaks down the information handling problem into a number of aspects.

User Requirements

The request forms supplied by the physicians are the instructing "programs" which obtain a particular processing for the raw data supplied (the blood sample) and then allow the result to be returned to the physician. Extra data may be supplied - provisional diagnosis, recent drugs - to allow an increased degree of error-checking or interpretation by the service. Without some clinical data, only the most extreme or general errors with assay processing can be detected before the return of the assay results. The physician seeks the maximum amount of information from the service, but to obtain this the service must have some knowledge of the patient's state and a clear idea (model) of the physician's decision-process which increase the data processing costs for both service and physician.

The Data Link

This is the actual "hardware" - forms, samples and delivery services - that carry the request and sample. If extra data flow is being considered then either some greater information "return" is required or an alternative link must be designed to reduce the load upon service and physician. These loads appear at the interfaces with the data link and the operations which must be carried out tend to define the physician's view of the service. This appears not only in his clerical input but in the value of the output which might consist of response time, error rate, intelligibility and the clinical value of the final result. Equally extra data transfer involves greater effort at

reception both in data capture and in the production of results.

Assay selection and pre-processing describe the initial part of reception's task. After checking that the request is correctly made out and the sample is adequate, an assay is selected. In the case of the thyroid assays, unless the physician had over riding authority, a fixed sequence of testing is followed. This strategy (Britton et al, 1975) is described in more detail in the next chapter. The blood sample is processed by spinning, followed by the transfer of plasma from sample to the assay tubes, their identification, batching and temporary storage. Finally the request forms, now with labels corresponding to the tube identifiers, are stored in a "current jobs" file. Job management is restricted here to the instructions to technicians processing the assays and updating records. For this, the technicians worksheets are produced for each assay, a single entry per sample, which also includes the sample identifier number together with relevant clinical data for an immediate check of the results by the technician. Monitoring the job queues and the technicians' work load could also be included as a management task. The assay results on the worksheets, together with the request forms, are then brought to the supervisor who authorises their transfer to the request forms and dispatch. Interpretation of the results is currently confined to detecting errors or doubtful results which suggest the need for either repeated or further testing. Equivocal results can be passed across to assay selection where the actual choice of assay is made. These steps are described in a flowchart form in figures 3.6 and 3.7. The final task for reception is to perform a last check on the returned forms and ensure their dispatch.

In the longer term, the sample stores hold any unused plasma in case of the need for further or repeat assays. The completed worksheets are filed by the Departmental Secretary in case of an enquiry (lost results) or for subsequent statistical use. This access is independent of reception, a written or telephone enquiry going directly to the secretary who must use the date and patient identification in order to locate the correct results.

Each stage can be analysed in terms of the information handling tasks involved. Figure 3.8 showes the similarity between reception and the information handling undertaken by an 'intelligent' processor or job manager assigning tasks to a number of specialist processors. These aspects often receive comparatively scant attention by staff who tend to

emphasise optimisation of assay precision or 'accuracy' (Holland and Whitehead, 1974; Ingelfinger and Goldman, 1976; Reece and Hobble, 1976). Other workers have taken an operations research based approach to laboratory management in a wider sense than envisaged here. In these studies throughput was emphasised rather than information content and, even where automation was applied to increase laboratory capacity, the twin problems of increasing requests and difficulties in interpretation remain. The automation of assay procedures had indeed reduced the unit cost of tests but it has also encouraged the use of "batteries" of tests. These present their own problems, particularly in the generation of false positive results. Finally this operations research work emphasised that though throughput could be made more efficient, demand would continue to rise until saturation occured unless other constraints upon requests appeared - such as the frequency of appearances at a clinic or the frequency of ward rounds. This work also failed to consider the problems of interpretation (that might help stimulate demand) for physicians using the service. A distinction seems to be neccessary between ambulatory out-patients/in-patients, and elderly patients if the importance and significance of a particular thyroid assay results are to be fully understood.

Assessment of the clinical value of a test result is made difficult by uncertainty as to the effect upon therapy - what action would have been taken without the result for example. Test results appear about a week after the consultation at which therapy was prescribed, set and the test request made. An unexpected result might instigate a letter modifying therapy or changing the date of the next consultation. Some results, though important, might not be considered sufficiently urgent for action before the next consultation, while others are useful simply to confirm clinical opinion or give some indication of a biochemical trend. To assess these results there is a need to define the information supplied by an assay result and then a need for a procedure to measure this content, routinely, in service operation. It is suggested that the control analogue can be used with models of patient behaviour, to define the value of these results. This depends upon the ability to accumulate reliable time-series data on these patients. Enhancement of the assay service to allow routine collection of limited records on thyroid patients is discussed in the next section.

3.10 Enhanced Operation of the Thyroid Assay Service

The thyroid assay service is a location where data processing experience and hardware coincide with data flows from a wide range of patients and physicians, and a need for a more effective use of these facilities. The costs of introducing further data capture and more sophisticated processing may therefore be comparable with the benifits of a more rational allocation of tests and improved clinical information.

The clinical statements of an experienced physician probably represent the ideal form of data collection and though a "human factor" in the physician-patient relationship is sometimes invoked to explain the mediocre performance of algorithmic diagnosis, it is assumed that these statements reflect the best observation of the patient state available. The difficulty then becomes the accurate aquisition of these clinical statements in a way acceptable to the physician. Direct interaction with the service, and hence with the thyroid disorder records, would be preferable for physicians within the hospital and would involve considerable cost in hardware and considerable effort in software provision. Attempts to introduce on-line medical records on even a small scale have indicated the difficulties of data-capture and the need for extremely reliable hardware and software. Eventually extensive machine held records will become feasible at low cost - but implementation for the near future is likely to concentrate upon locally developed, distributed data-bases.

Despite the above objections it is suggested that the assay service could currently establish a limited data-base, if suitable data- capture is possible. Physicians using the service are accustomed to the need to supply data and are protected from the complexities of machine operation and from the immediate effects of machine failure by their lack of direct contact. The pivotal role in data handling of reception indicates its importance for changes in processing as envisaged by figure 3.9. Three areas of extended processing can be isolated: assay selection; interpretation and presentation of results; and the handling of patient assay records. To complement these functions, a new data link between physicians and service is required if additional or more reliable data input is to be obtained without excessive clerical demands upon service or physician. Implementation of an 'extended' assay service is discussed in the following sections but the emphasis is

placed upon confirmation of the basic concepts rather than production of a working system. To test the feasibility of the key component, an acceptable data link between physician and laboratory, a pilot study has been undertaken. The results from the pilot sudy form the background to chapters 4 and 5.

3.11 Changes in the Assay Service Reception Operation

The collecting of patient details is already a part of the production of the worksheets. As extra clinical data are being considered, a trade-off is required to exhange the clerical effort of inputting data for automatic production of the duplicated worksheets. If extensive clinical data are required, then forms allowing optical mark reading will reduce the labour for both the service and the physician. Reception continues with the sequence described: input of requests, periodic production of worksheets, updating with results and possibly further assays as indicated by the strategy, and finally the regular output of results for return to the physcians. Additional functions require software to carry out routine "house-keeping" upon the patient data-base archiving, hard-copy backup, machine-held backup, and the ability to supply records and operational statistics for occasional secretarial interrogation. Hard copy records ensure reliability and allow a manual system to take over in the event of machine failure. Assay selection and interpretation are required during input, update and output. The software used depends upon the form of the patient records, the availablity of time-series data and the complexity of the models or algorithms applied to the data base. Initially only the current record will be considered. Time series data allow not only more sophisticated processing but the output of a complete synopsis of previous measures with each new assay result. Figure 3.10 indicates those functions which service or are dependent upon the proposed data base. Figure 3.11 shows the relationship between the data flow available and the level of data processing possible.

The process of inputting data involves the same operations as before except that data are written via a terminal to the data-base rather than being typed directly on to the worksheet. Software checks of patient identification, assay type and number are used to reduce errors and some advantage can be taken of automatic defaults and tabbing to reduce effort (e.g. most patients are female). The above details cannot be made machine-readable but the physician's identification and

"address" can usually be limited to keying in initials, and the clinical data may be made simple or even machine readable. Input records are duplicated in a worksheet file and sent to the printer as required. The practice of using three labels with the assay number to link sample, request and worksheet probably remains the most convenient, though now the assay number must be keyed into the record. This need only be set at the beginning of each session as the sequence number for subsequent assays can be indexed automatically. The full record is finally displayed and checked before being added to the end of the patient record file. Assay selection occurs at this stage. The current record is examined on the basis of the strategy used to select the test.

Records awaiting results can be detected by the lack of a result and picked out individually by their assay number. They can be recalled for checks and the input of results taken from the worksheets. Results are loaded in batches as an assay is completed and a decision on further testing made, possibly automatically according to the strategy used (Britton et al, 1975) or other algorithms. Up dating may be conveniently timed to allow concurrent output and signature of the forms by the supervisor. Output of results is via a normal A4 size matrix printer and includes the current patient record and result. Presentation is of course a matter of local preference and can to some extent be modified to meet specific requirements. The A4 sheet can be fitted directly into the medical record and as long as time-series records are maintained, the updated synopsis can replace the earlier one. This removes the inconvenience of collecting together the smaller forms with individual results by using a single sheet which can be replaced if lost. Graphical output could also be supplied - either giving results and treatment against a time axis or, when simultaneous measures exist, patient trajectories through 'hormone space' (figures 3.12 and 3.13).

The data base is realised as a disk file with records stored sequentially as requests appear. Records are archived as space is taken up, and record movement is avoided by using a circular file (figure 3.14.) Records from the same patient can be linked by chaining records back in the sequence of their appearance. The latest record for the patient has the location of the previous record for that patient. As time-series files require on-line sorting of the contents to check whether a patient has appeared previously, it may be necessary, because

of core size and sorting time limitations to sort only the patient identifications in a separate file. The patient I.D. file is a directory locating the latest record on that patient. The advantages of searching a special identifier file depend upon the proportion of requests without a history.

In the event of a machi ne failure the manual system can be reactivated. The request forms, normally disposed of, are returned with the results and worksheets typed up as previously. The worksheets are retained to bring the machine files up-to-date or restore any loss. In the long-term, protection is provided by backing-up disks.

3.12 Data Link Design

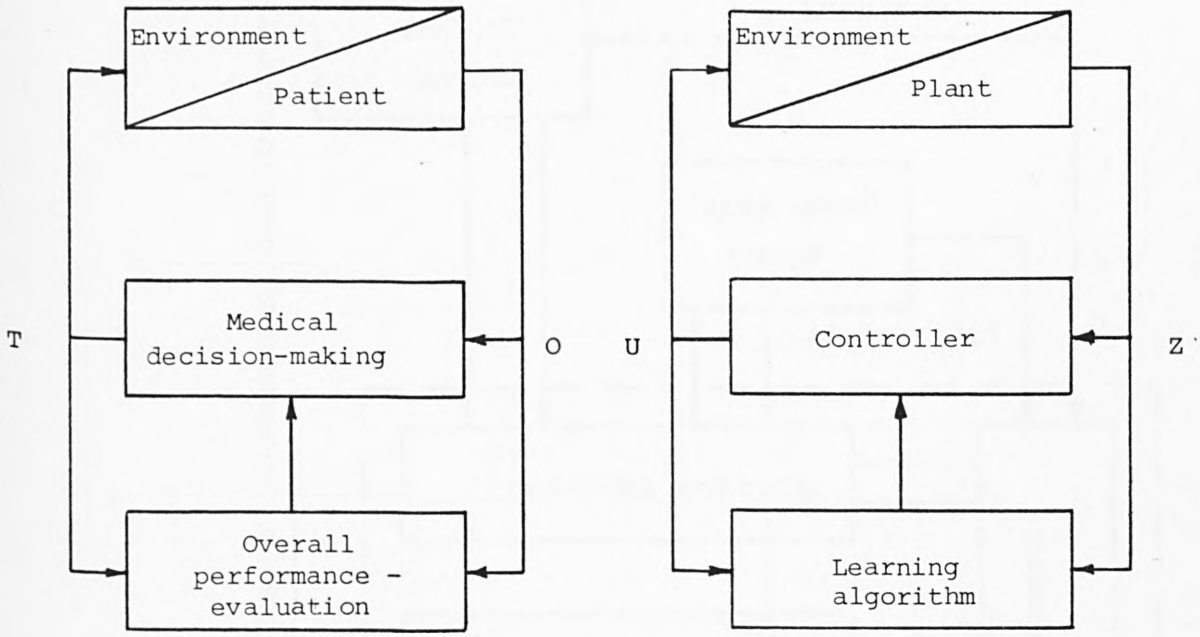
A number of options for the data link were considered. Ideally it should be cheap, flexible in terms of the type and quantity of data carried, reliable and acceptable to staff at both ends. The use of direct inputs such as "data-pads" or portable terminals may become feasible but at present the medium must be postal delivery of forms and samples. The fact that the service handles different types of test requiring differing data flow creates difficulties since a special format for each test is not acceptable. Different levels of data flow allow changes in the possible action by the service. Figure 3.11 shows the kind of range possible with thyroid assays from the minimal flow for the simplest operation to the richest flow where extremely sophisticated processing could occur. A number of methods have been considered for the data link which would allow a range of test requests and data to be carried via a standard form which meets the administrative requirements of the hospital and Supra-regional Assay Service (S.A.S.). An example of modifications to the existing hospital and S.A.S. forms is shown in figures 3.15 to 3.17. Figure 3.15 shows a 'ring binder' containing standard hospital forms over which test-specific masks can be dropped. The spaces in the masks allow the user to tick appropriate boxes for each request. Figure 3.16 is a similar device for use by S.A.S. laboratories. This time a cheque book format has been used. Figure 3.17 shows an example of the layout of the general form and a thyroid request mask for the cheque book format. In each case the aim is to produce an easy to use machine readable route for clinical data. The optimal data link would allow direct interaction with the data base and remove the need for request forms altogether. Though currently impracticable the recent growth in micro-computers suggests that large

numbers of (and hence cheap) local area networks will soon be in use.

For the purposes of the pilot study a less ambitious format was chosen. Figure 4.4 shows the request form used. It is an extended version of the standard hospital request form which allows a fixed set of clinical data to be easily supplied. The selection of the particular clinical signs is discussed in chapter 4. The form has three overlayed 'flimsies' which allow duplication of the request if more than one test is required. In the manual system the request result is written below the patient I.D. and the form may be gummed into the medical record in an overlapping sequence which allows easy reference to previous therapy and results (see figure 4.5). This form was tested during the pilot study discussed in chapter 4 and subsequently underwent minor changes.

3.13 Implementation

Use of the control analogue and the information-handling analysis have provided a useful framework for a discussion of possible improvements in the management of thyroid patients and assay service operation. The possible developments of management through pattern recognition and control techniques were, it was argued, heavily dependent upon the routine provision of reliable, precise clinical data. The limitations of earlier algorithmic work and the difficulties of obtaining clinical data on chronically ill patients directly led to an examination of the assay service as a possible location to capture limited amounts of data at low cost. A proposal was made for an alternative operation which would generate a suitable data-base. It remains to be shown, before development of the software and implementation, that the link suggested can provide data which will really be useful and which, most importantly, will be acceptable to the physicians who use the assay service. This has led to a pilot study to determine the quality of data which would be provided and its immediate value for the selection of thyroid assays. The pilot study will also give valuable general experience before a final system is proposed. The study is described together with the basis for the selection of the particular clinical and biochemical data collected. The success in using this data in an extension of an existing strategy for test selection is described in chapter 4. An additional reason for the pilot study was to examine whether, as has been suggested, particular patient groups can be discerned in the patient population indicating a need for more detailed interpretation of results. The characteristics of the sample studied are examined extensively in chapter 5.



Medical system

Plant control system

T - Treatment

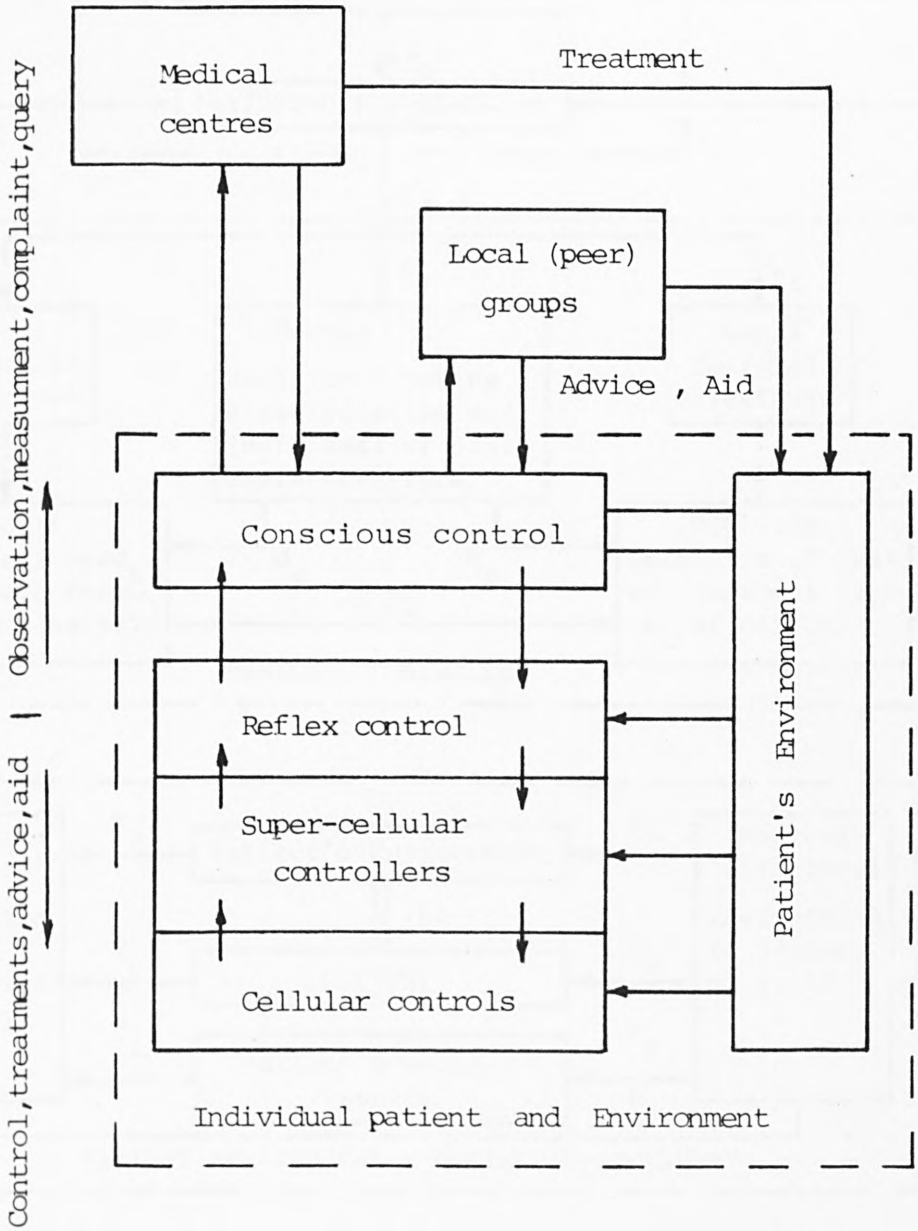
O - Observation

U - Input

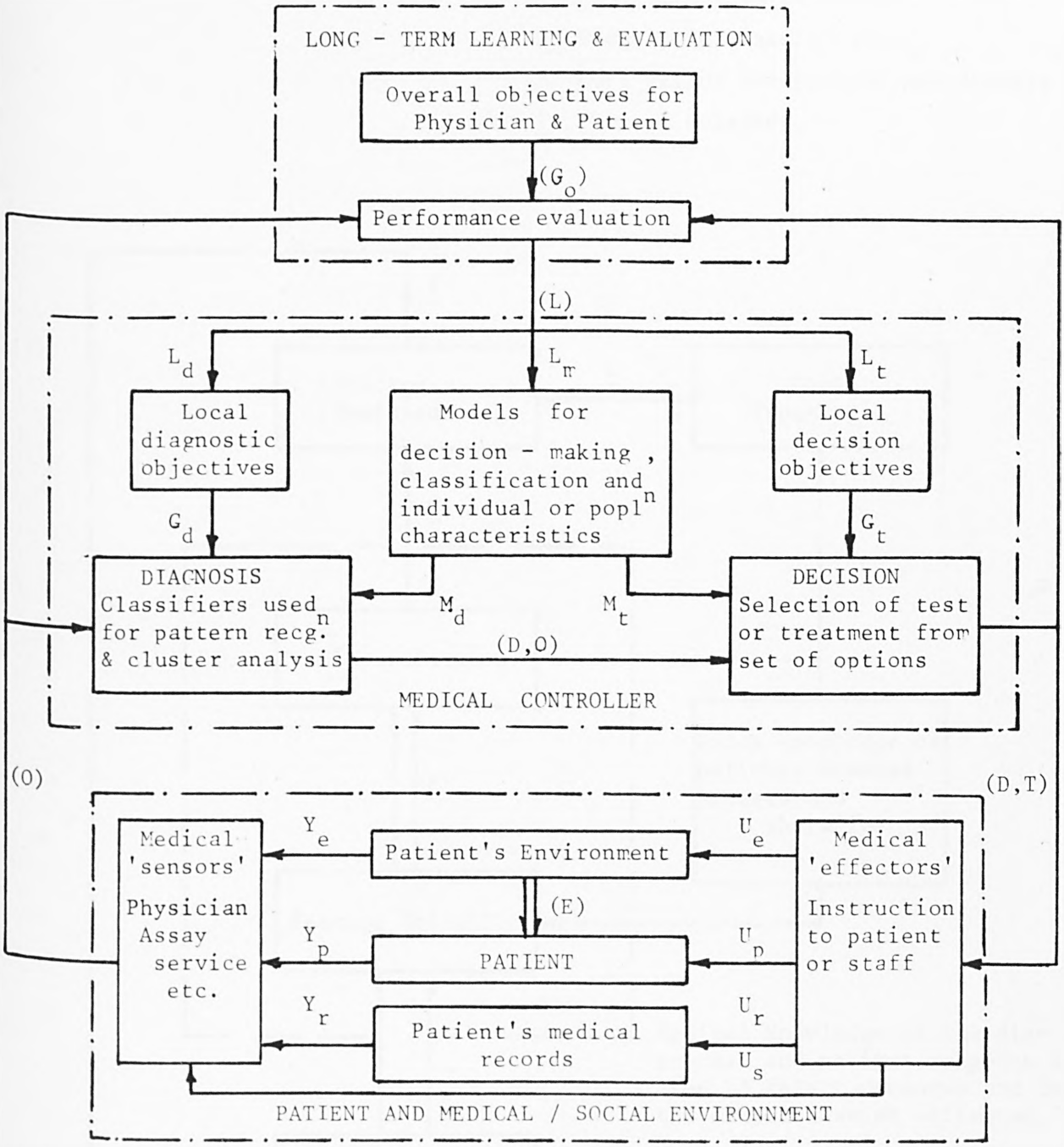
Z - Measurement

The physician-patient relationship viewed as a control problem

Figure 3.1



Hierarchy of control in health care Figure 3.2



(O) Observations of patient ,environment and recorded condition

(D) Diagnostic statement on patient

(T) Treatment selected for patient

(L) Learning input which modifies local objectives or models used

(G) Objectives of medical controller

(Y) Attributes of patient ,his environment or records

(U) Inputs to patient ,environment ,records or to activate sensors

Diagnosis and treatment viewed as a control system Figure 3.3

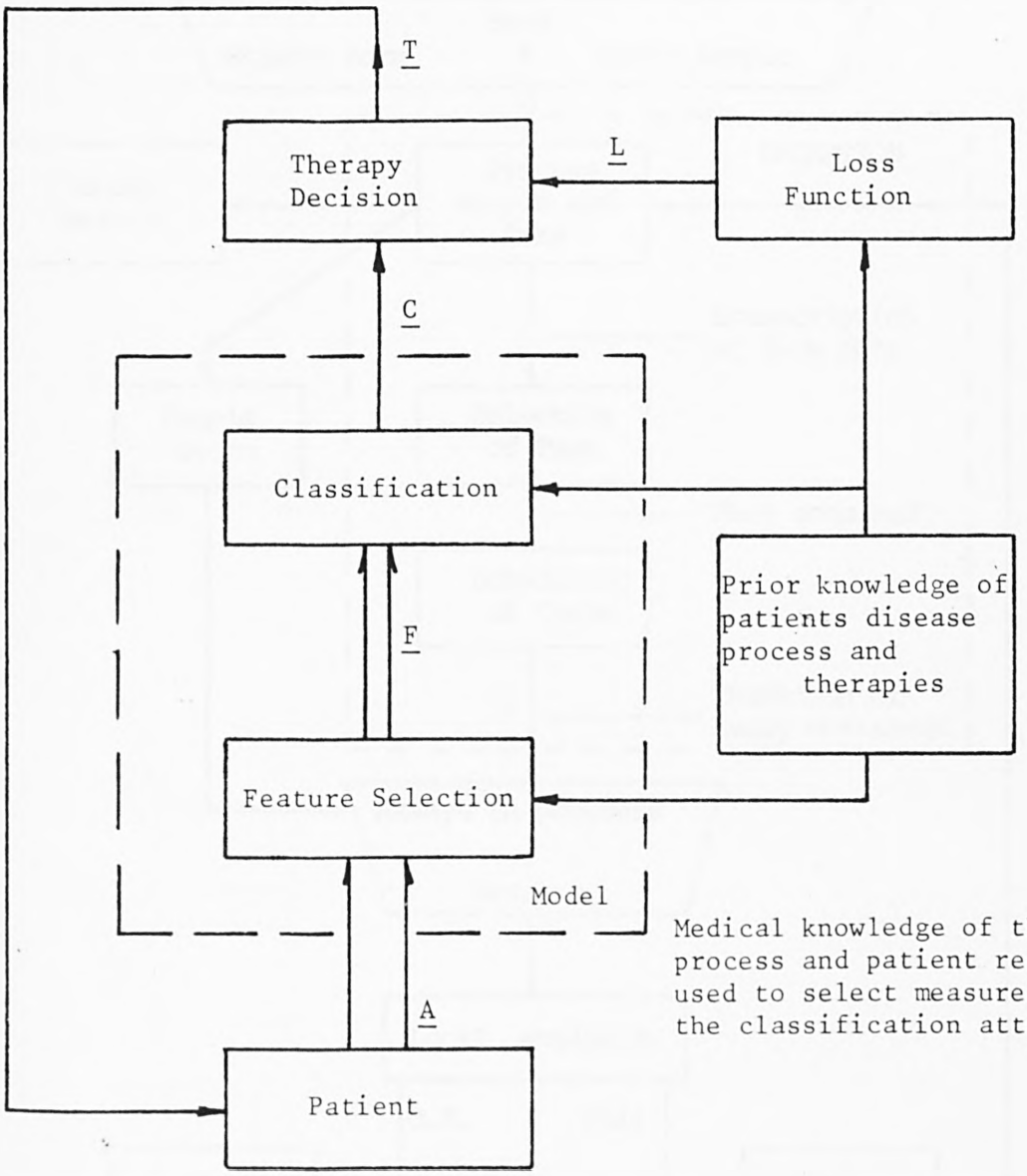
A Patient attributes, possible measures

F Features selected for diagnosis and therapy selection

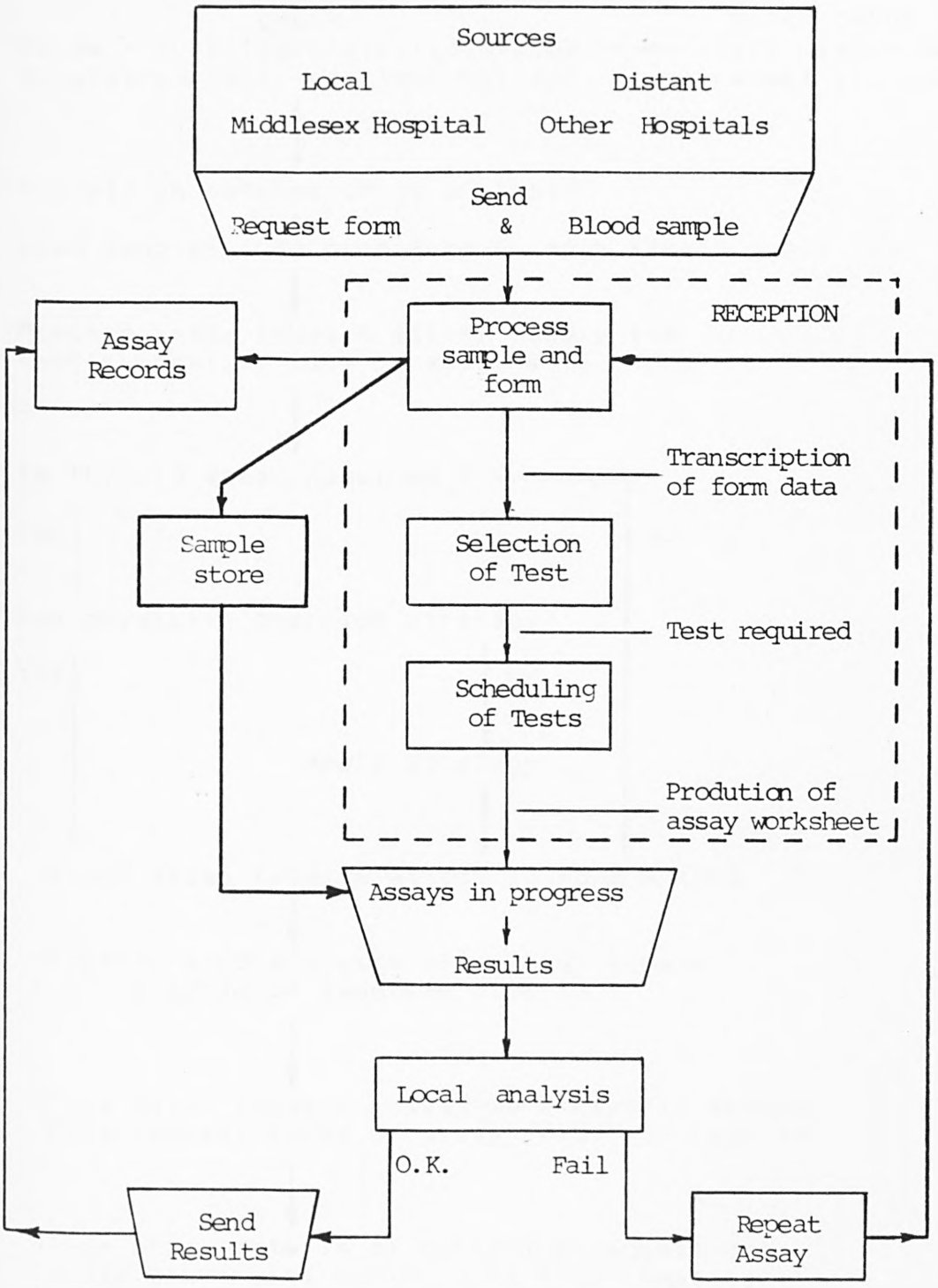
C Diagnostic classification

L Loss vector for patient and disease

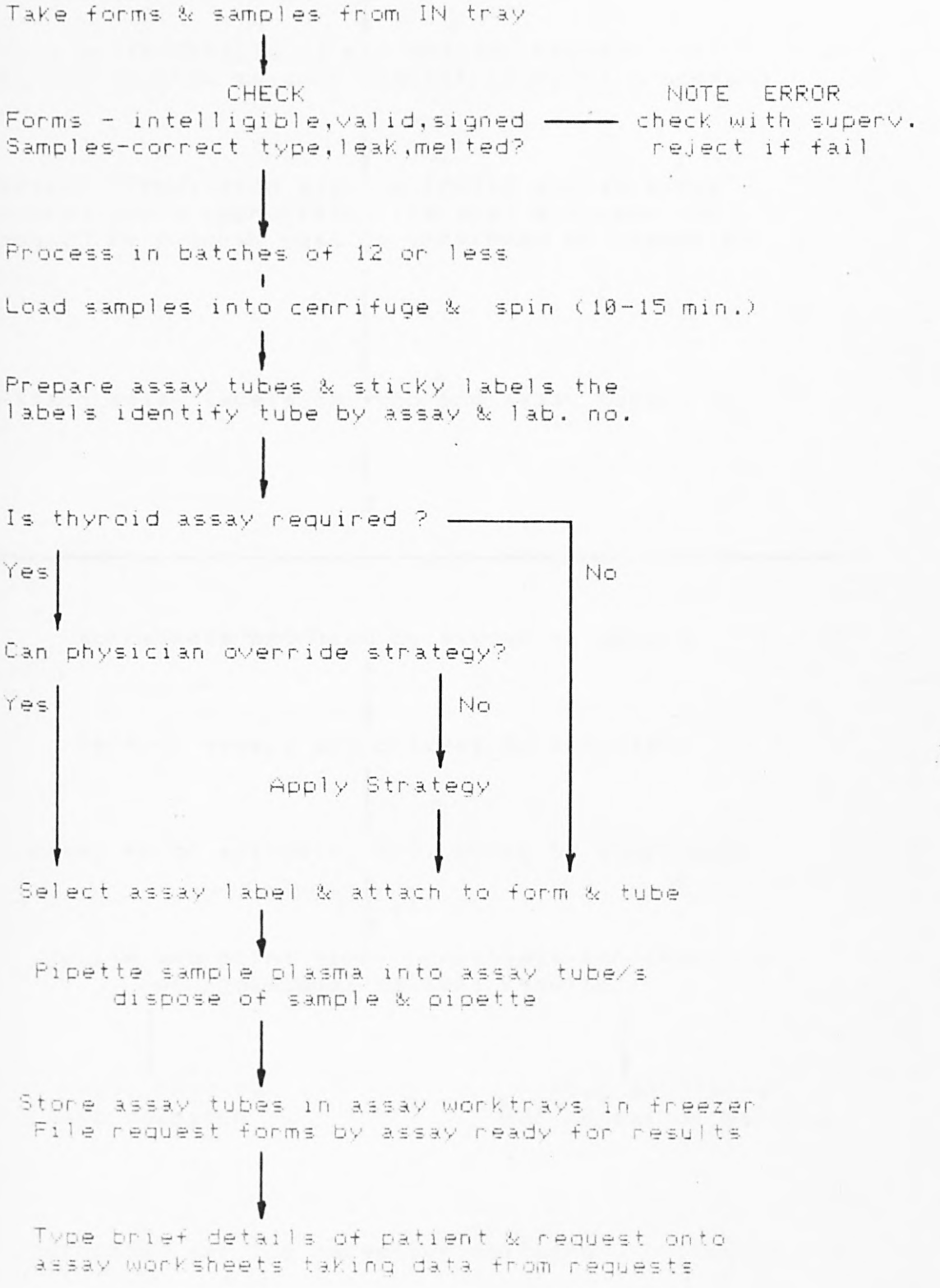
T Therapy selected



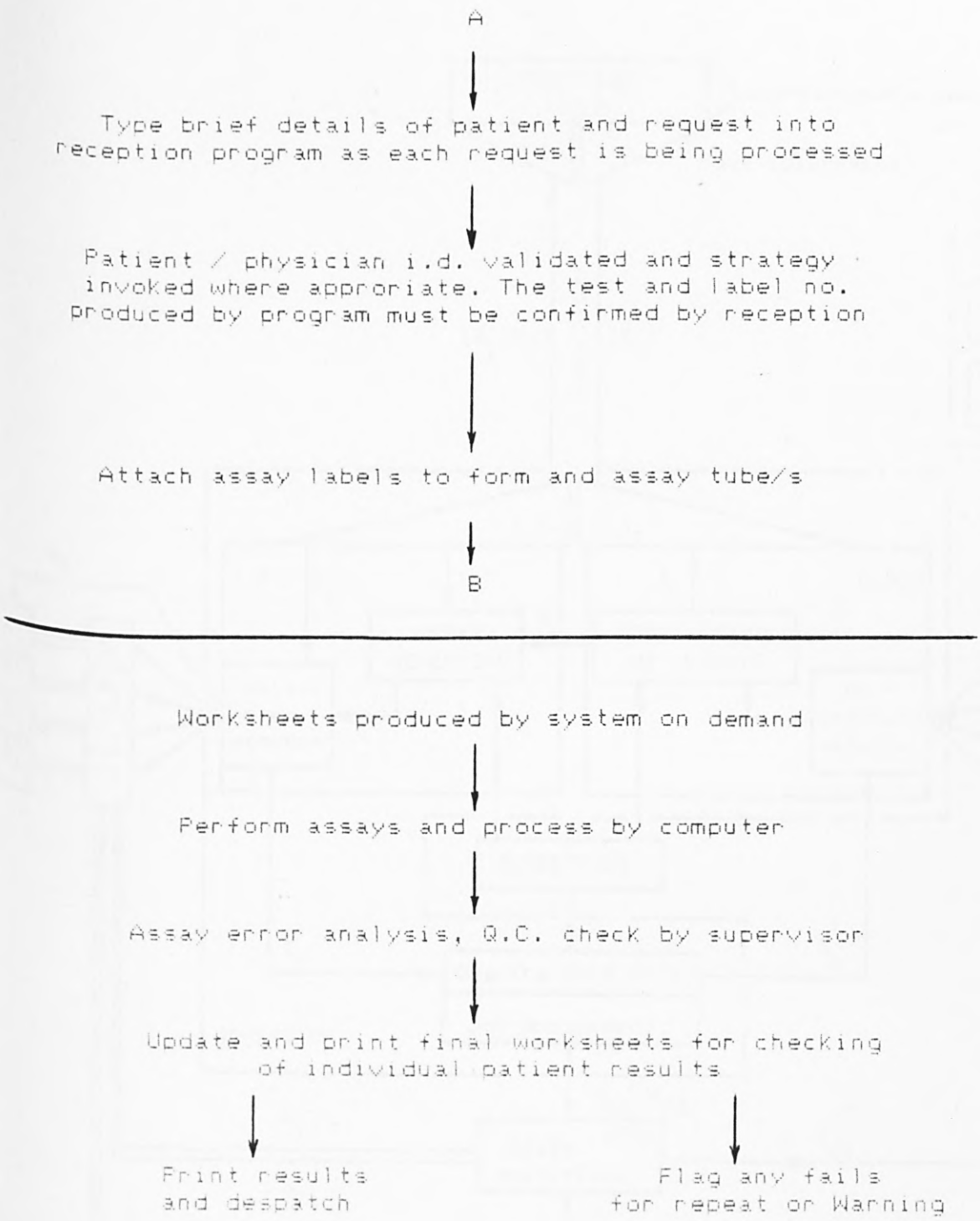
Diagnosis as a two level pattern recognition problem Figure 3.4



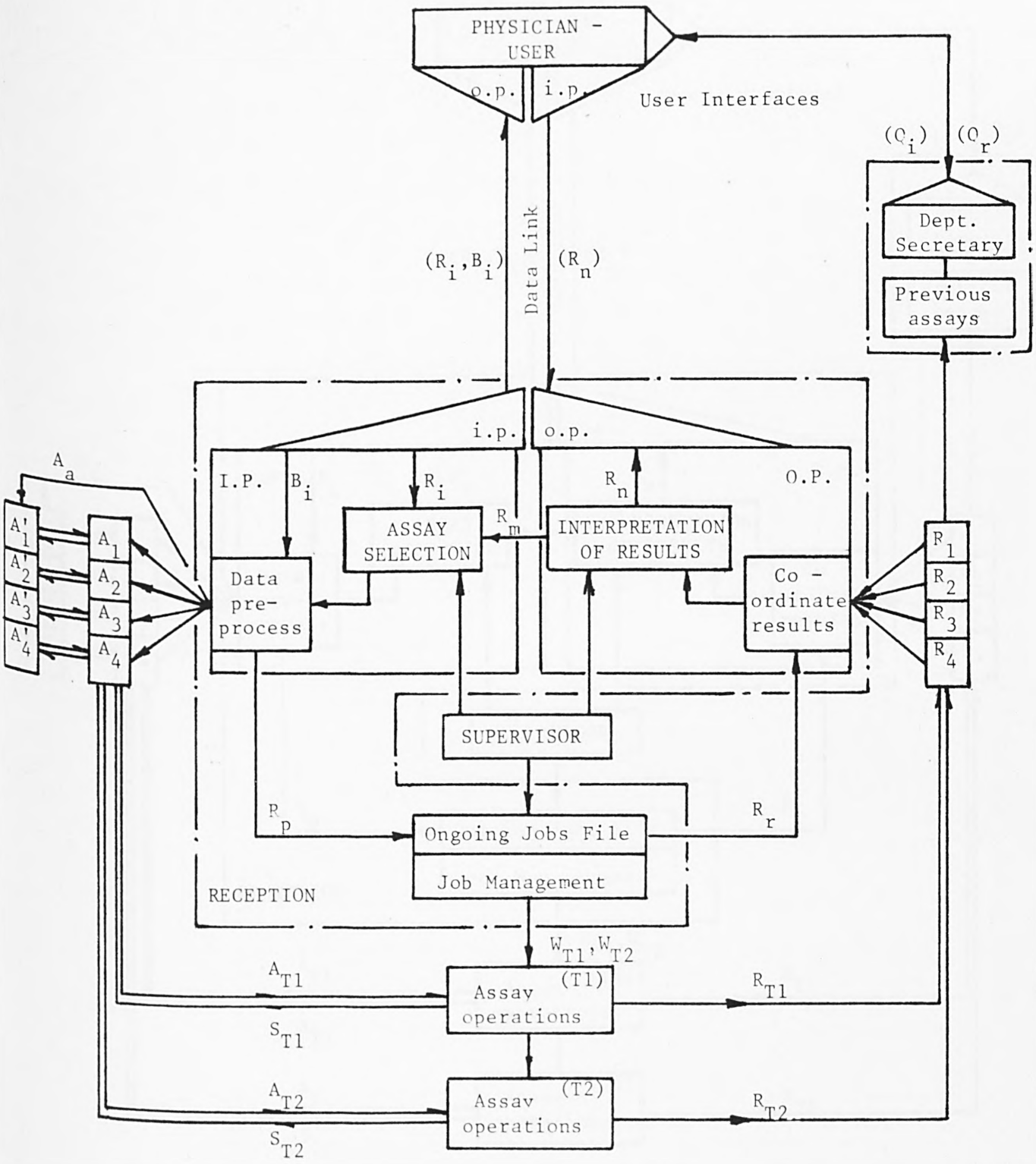
Existing service sequence of operations Figure 3.5



Sequence of operations by existing reception Figure 3.6



Extended service reception software Figure 3.7

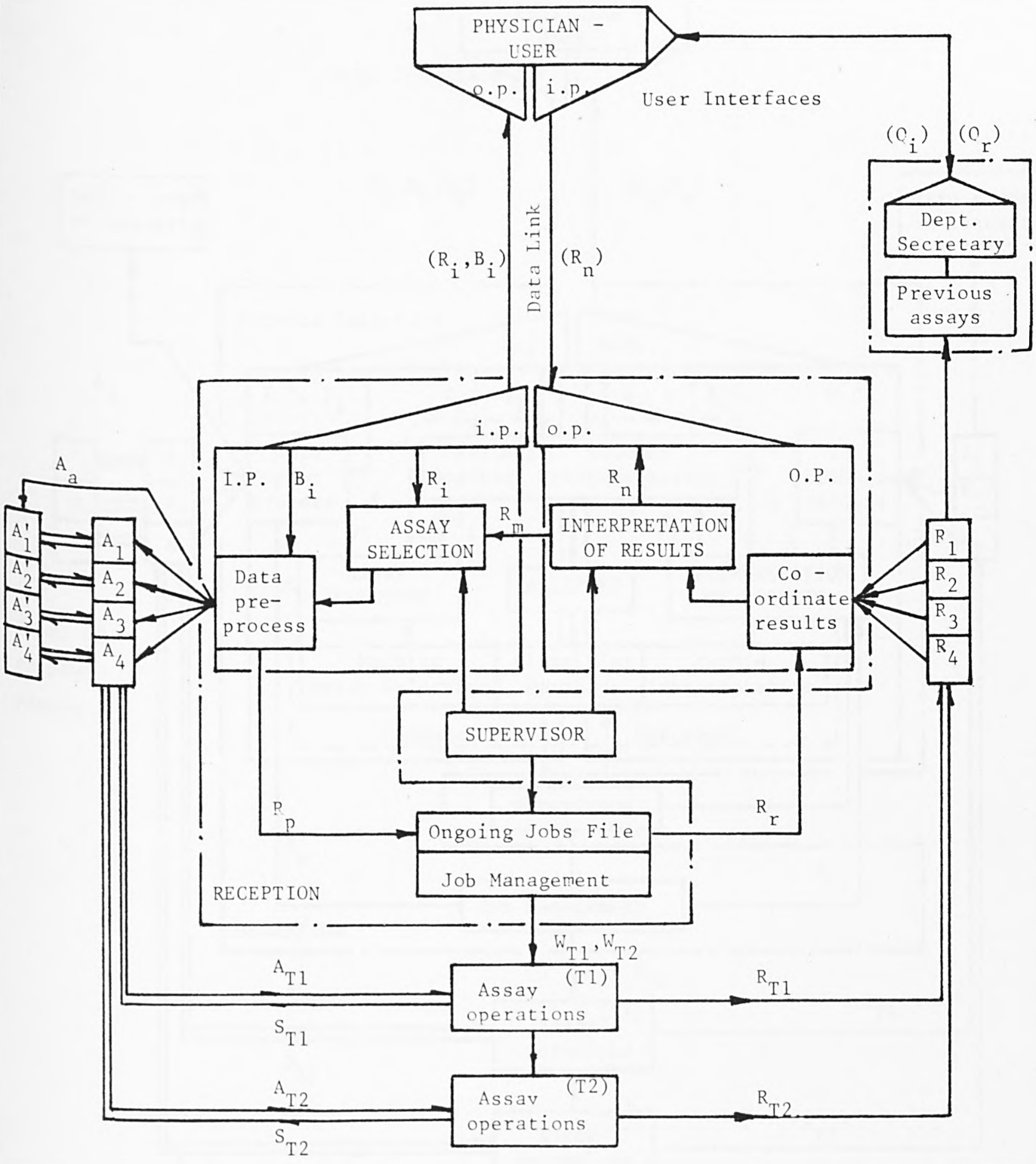


A_{T1}, S_{T1} Batches of plasma for assay (T1) and surplus plasma returned for long - term storage

R_{T1} Batched assay results on worksheets from process (T1)

W_{T1} Instructions to process (T1) on worksheet.

Information handling by the existing assay service Figure 3.8



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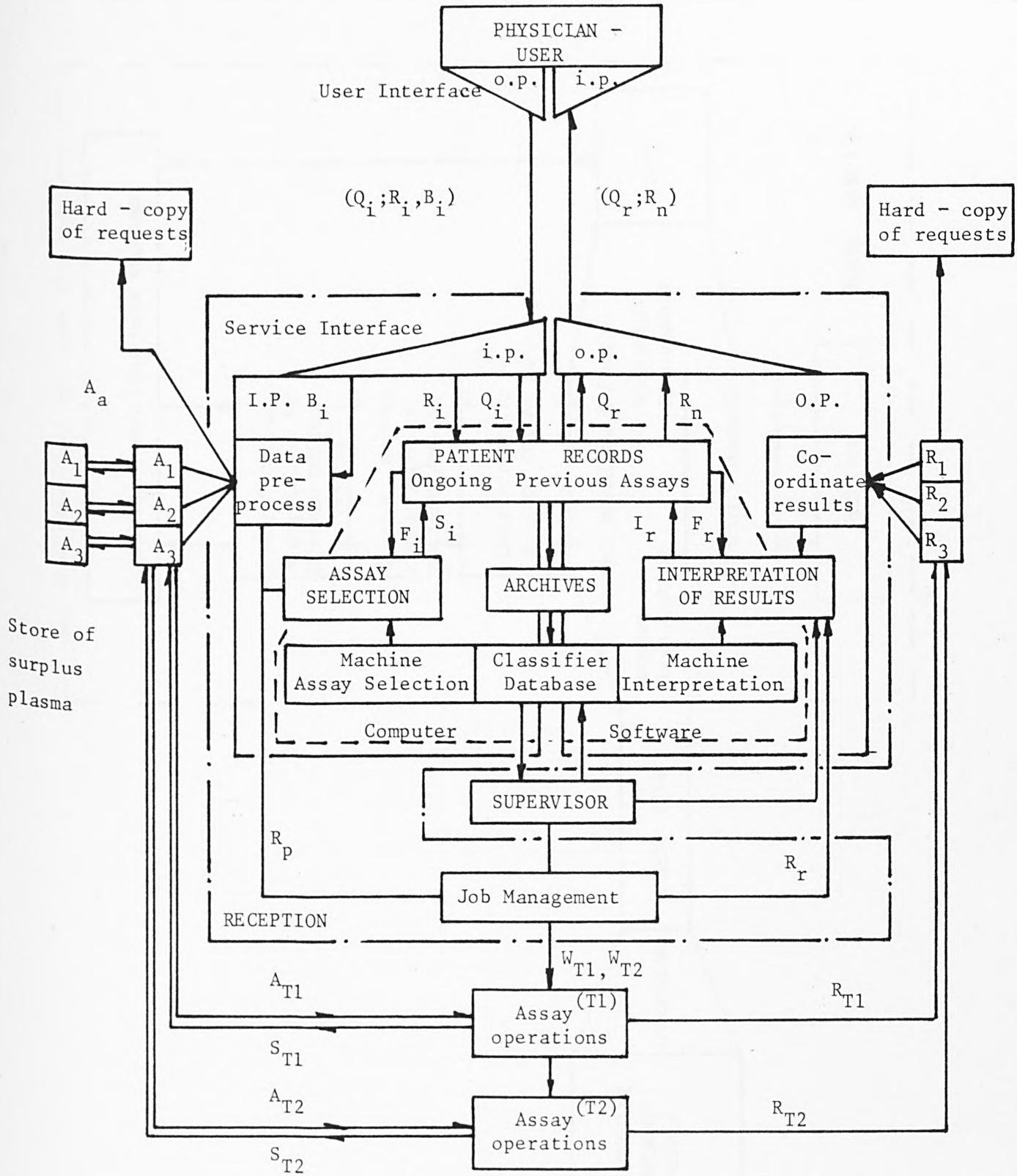
Information handling by the existing assay service Figure 3.8



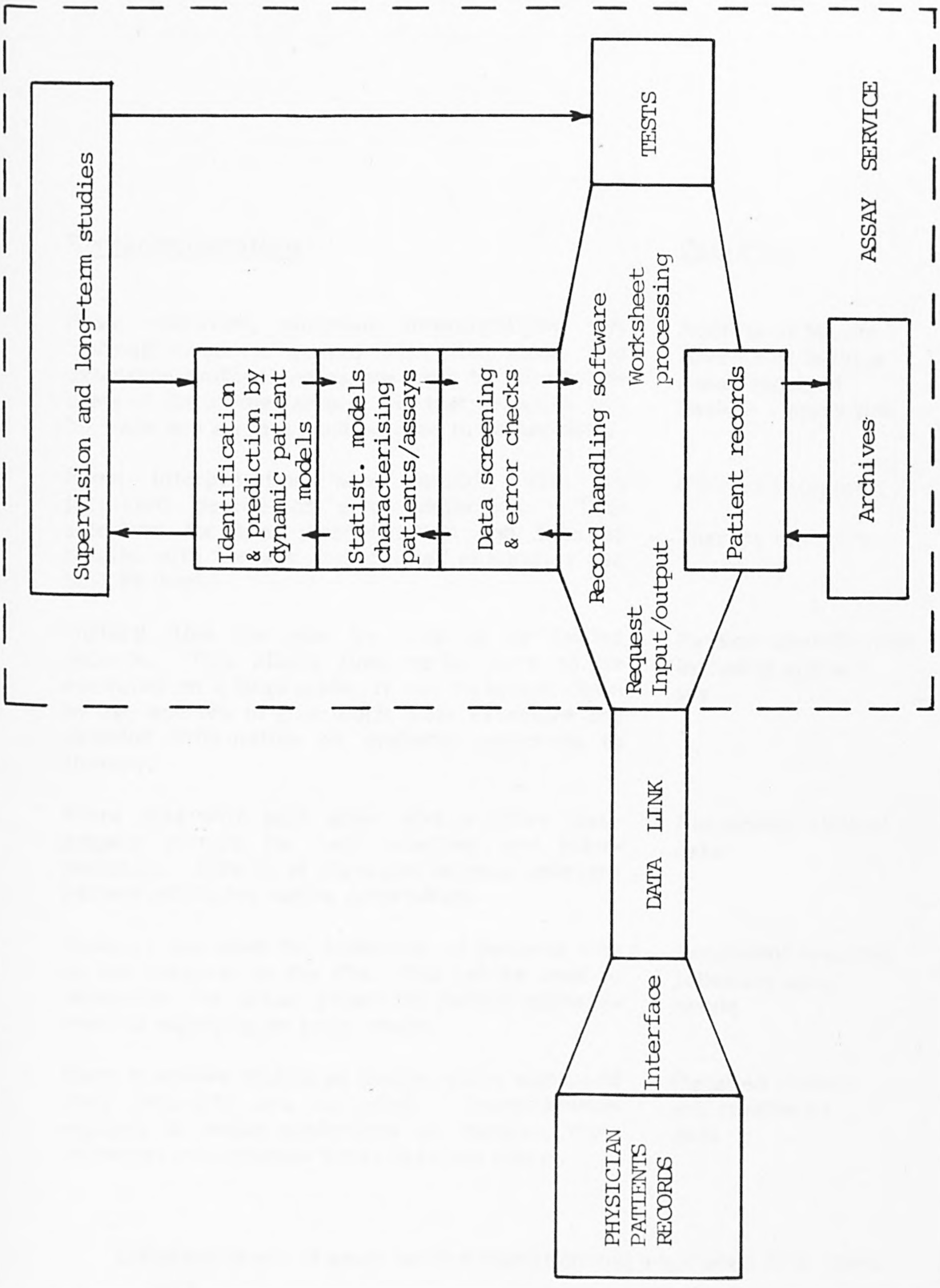
Q_i, Q_r Enquiries about previous assays

R_i, B_i Request instructions with clinical data and associated blood sample

R_p, R_r Assays required and results expected by the job schedule

R_n, R_m Interpreted assay results and repeated or further assays

Enhanced information handling for assay service Figure 3.9



Levels of data processing undertaken in an extended assay service

Figure 3.10

Reception operations	Data Flow
Basic operation, minimum interpretation. A 'normal' range is quoted with the result and extensive protocol notes are sent to inform the users of disturbing factors. No test selection can be made and surveys must be used to gather data.	Address of Source Address of Service Assay required Patient - assay link
Some interpretation now possible with an increased degree of error detection. Test selection for best discrimination and files of results with therapy and clinical categories can both be used.	Clinical category Therapy category
History files can now be built up by linking records. This allows time series data to be examined on a large scale. It may be broken down by age and sex to give much more extensive and detailed information on probable responses to therapy.	Patient identification including age and sex
Extra data with each assay give a richer nosographic picture for test selection and interpretation. Effects of therapies on most relevent patient attributes can be determined.	Augmented clinical data
Reduces the need for follow-up of patients who do not reappear on the file. This can be used to determine the actual effect on patient management of supplying an assay result.	Treatment response following assay result
More extensive models as dosage, extra signs, and their intensity are included. Interpretation expands to make predictions on dosages, their outcomes and optimum times between assays.	Detailed clinical and treatment data

Different levels of assay service operation and associated data flows.

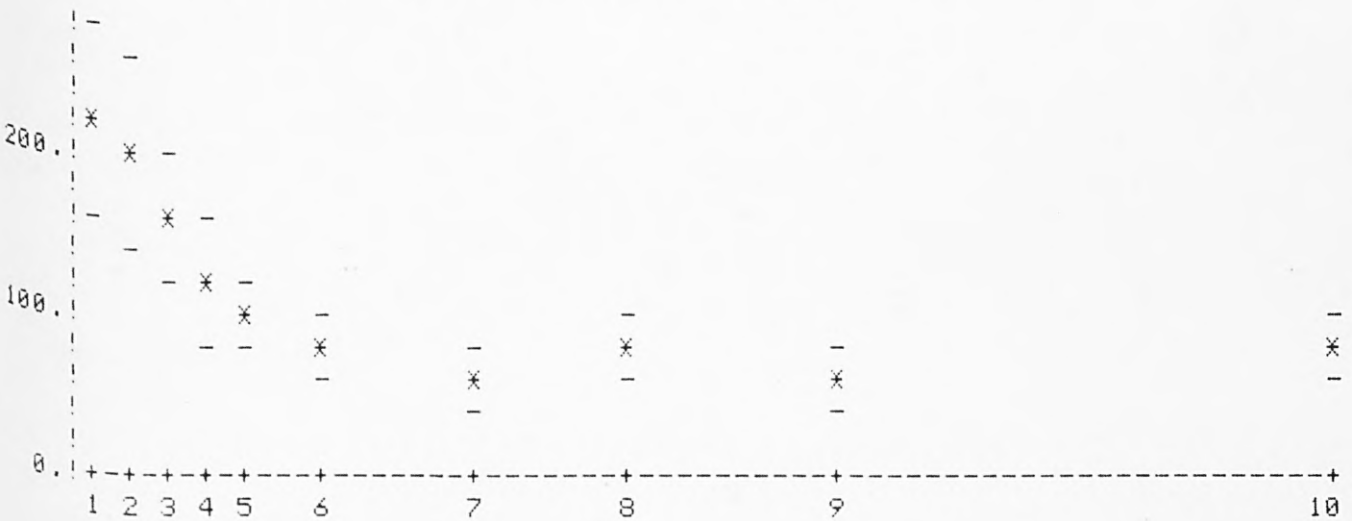
Figure 3.11

THYROID HORMONE ASSAY RESULTS Report:- 18/06/79

Name: Mr N.G. Persona Hosp. No. 11 22 33 44
D.of B. 13/07/60 Out Pat.

No.	Sample Date	T4 (nM)	T3 (nM)	TSH (mU/L)	Clinical comments	Drug	Dose
1	2/03/78	220.1	23.7		Def.hyper	None	
2	16/03/78	201.0			Def.hyper	Cbzl	45mg/d
3	30/03/78	156.3			Prob hyper	Cbzl	45mg/d
4	14/04/78	122.4			Prob hyper	Cbzl	45mg/d
5	30/04/78	105.1			Prob hyper	Cbzl	30mg/d
6	27/05/78	70.9			Prob euthy	Cbzl	20mg/d
7	28/07/78	55.7			Prob euthy	Cbzl	15mg/d
8	14/09/78	75.9	6.1		Prob euthy	Cbzl	10mg/d
9	07/01/79	60.4			Prob euthy	Cbzl	10mg/d
10	18/06/79	87.8	7.8		Prob euthy	Cbzl	10mg/d

Plot of T4 results (nM) against sample dates
95% confidence limits marked by '-'



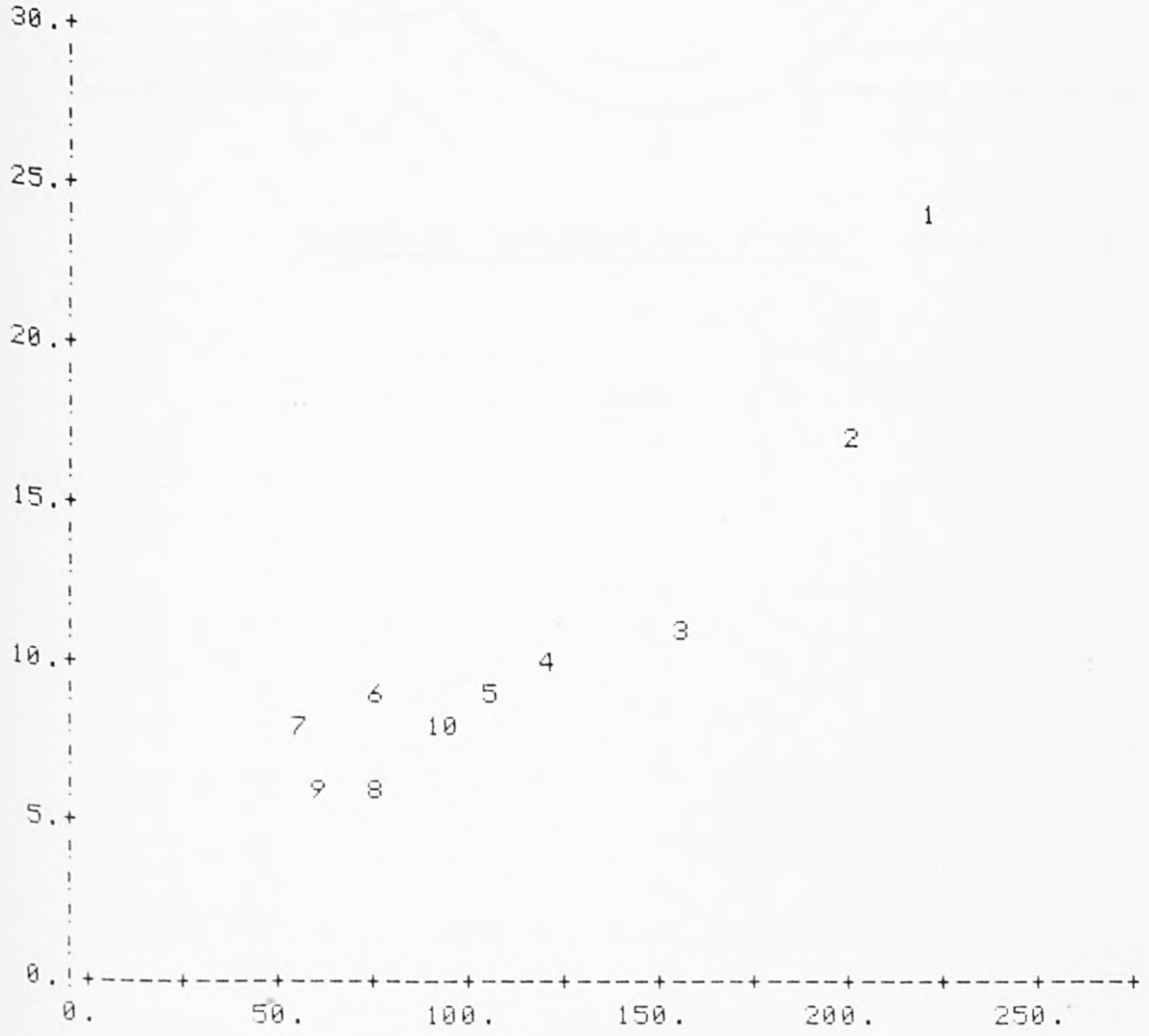
Example of report sheet for Thyroid hormone assays including clinical data from patient record. The plot quality and detail is limited by the use of 'character' graphics and most matrix or line printers now allow direct graphics dumps Figure 3.12

THYROID HORMONE ASSAY RESULTS Report:- 21/07/79

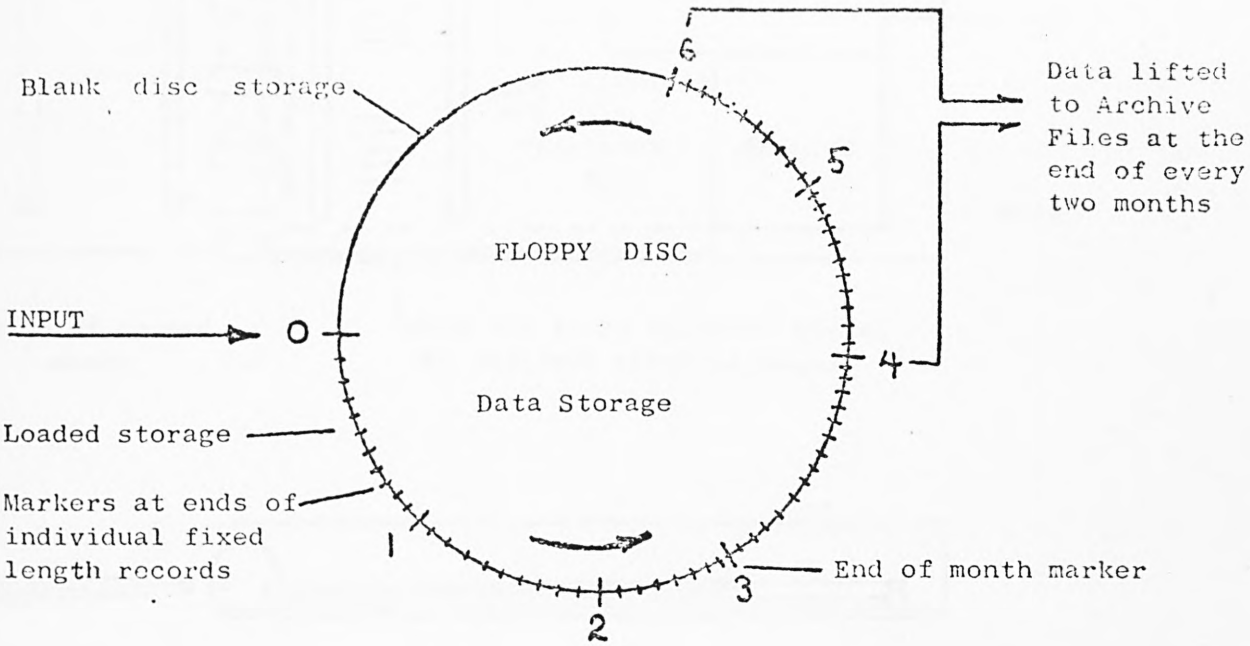
Name: Mr G. Personaa Hosp. No. 12 34 45 67
D.of B. 12/01/57 Ward 12

No.	Sample Date	T4 (nM)	T3 (nM)	TSH (mU/L)	Clinical comments	Drug	Dose
1	02/03/78	220.1	23.7		Def. hyper	None	
2	16/03/78	201.0	15.8		Def. hyper	Cbzl	45mg/d
3	30/03/78	156.3	11.2	0.0	Prob hyper	Cbzl	45mg/d
4	14/04/78	122.4	9.8		Prob hyper	Cbzl	45mg/d
5	30/04/78	105.1	9.1		Prob hyper	Cbzl	30mg/d
6	27/05/78	70.9	8.5		Prob euthy	Cbzl	20mg/d
7	28/07/78	55.7	7.6		Prob euthy	Cbzl	15mg/d
8	14/09/78	75.9	6.1		Prob euthy	Cbzl	10mg/d
9	07/01/79	60.4	5.9		Prob euthy	Cbzl	10mg/d
10	18/06/79	87.8	7.8		Prob euthy	Cbzl	10mg/d

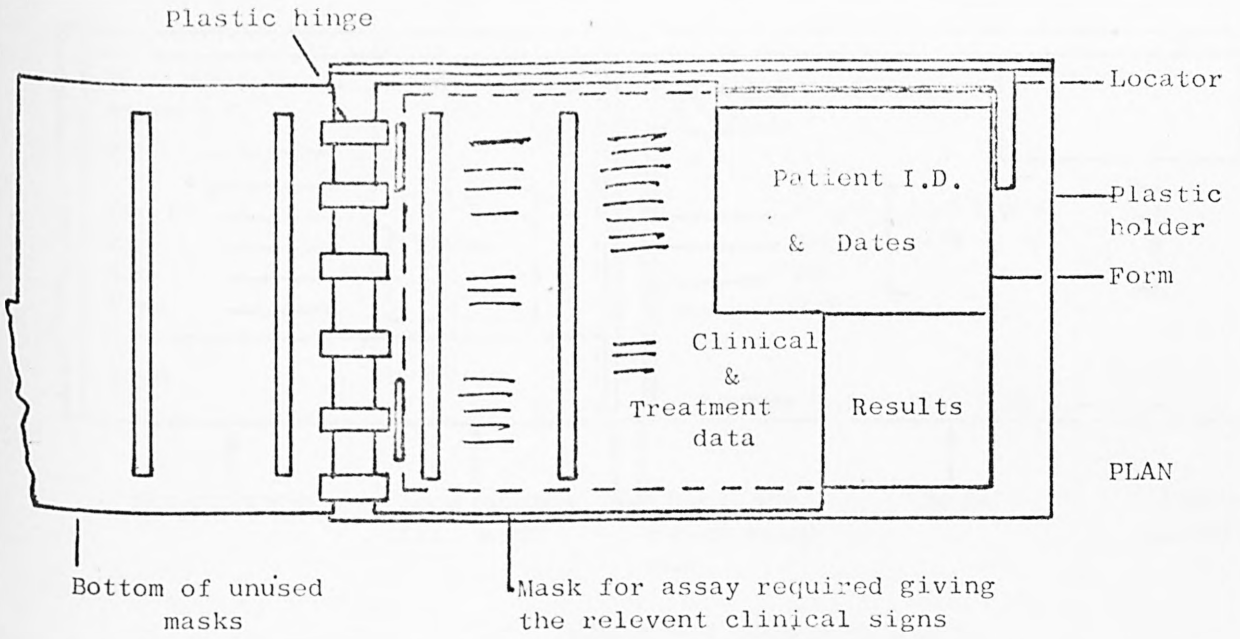
Plot of T3 results (nM) against T4 results (nM)
95% confidence limits marked by ! and -

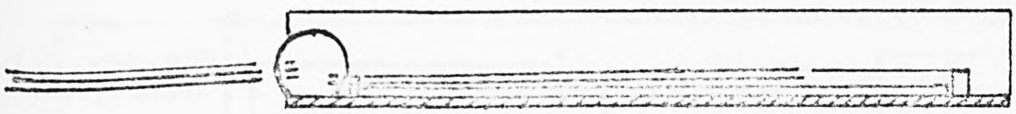


Example of report sheet for thyroid hormone assays including clinical data from patient record. The plot quality and detail is limited by the character graphics. Figure 3.13

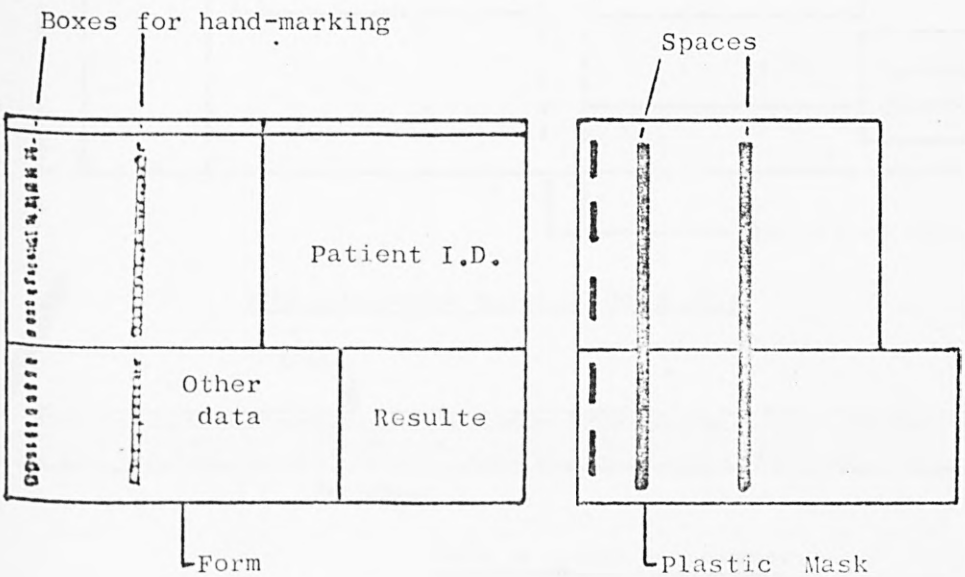


Cycling of Individual Data Storage Figure 3.14



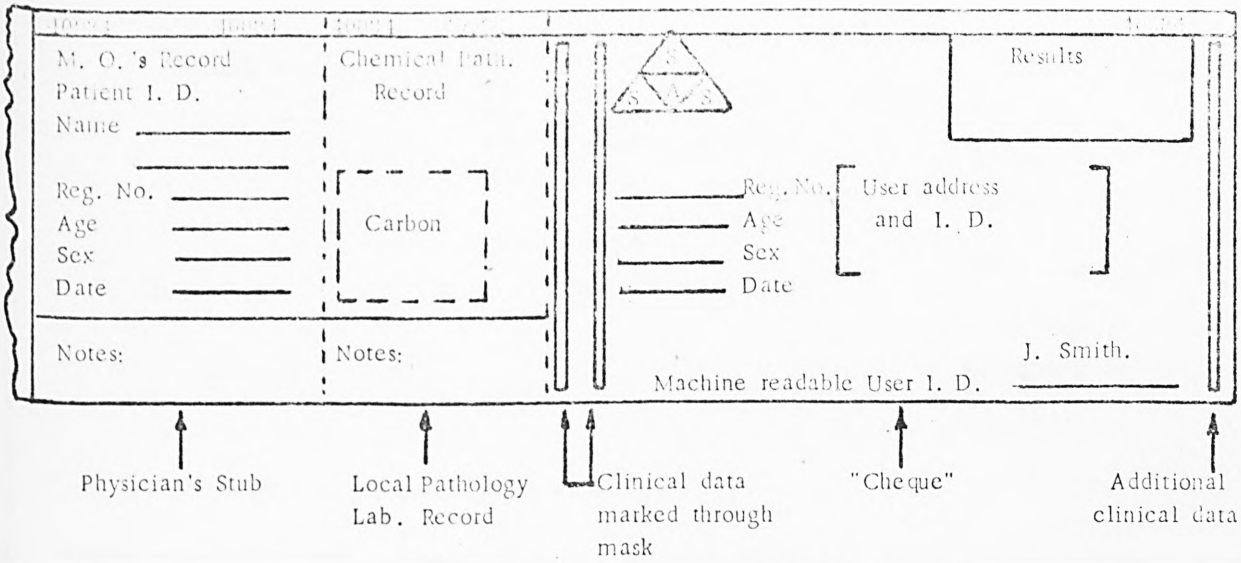


ELEVATION

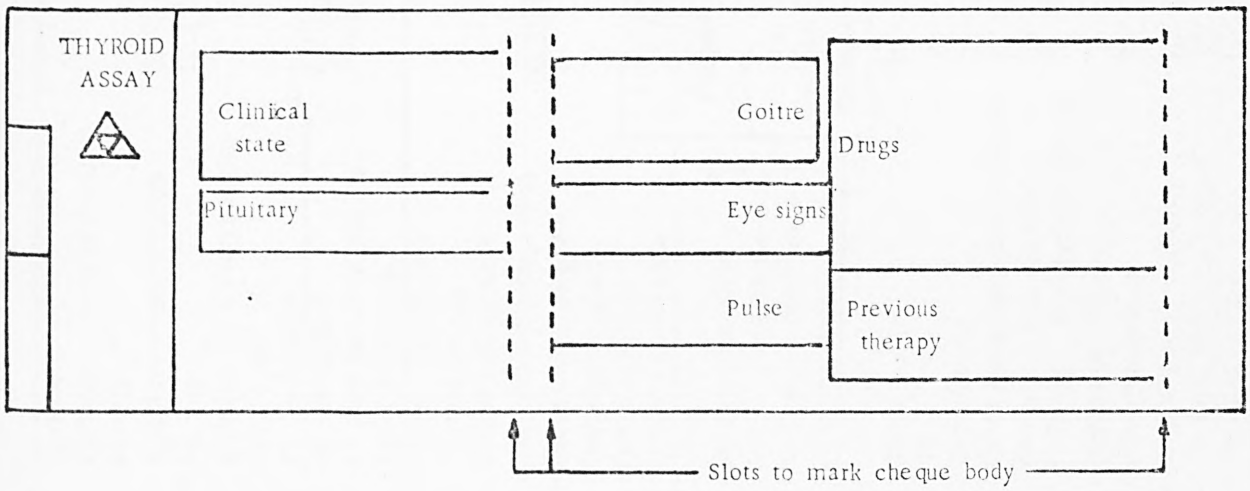


General form and masks for particular assays in a desk type holder

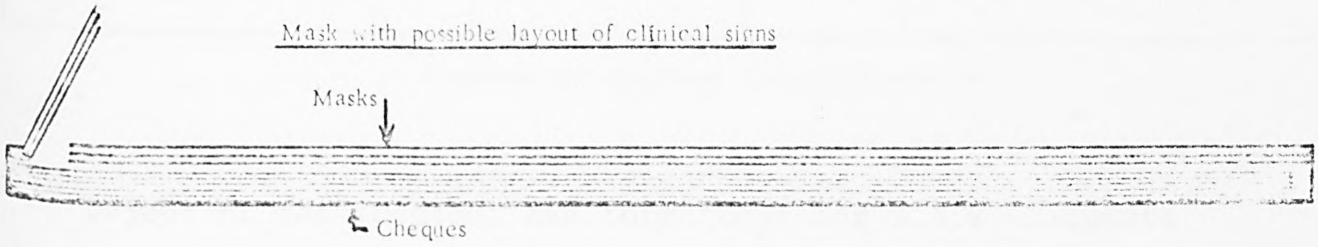
Figure 3.15



Cheque Face before being filled in



Mask with possible layout of clinical signs

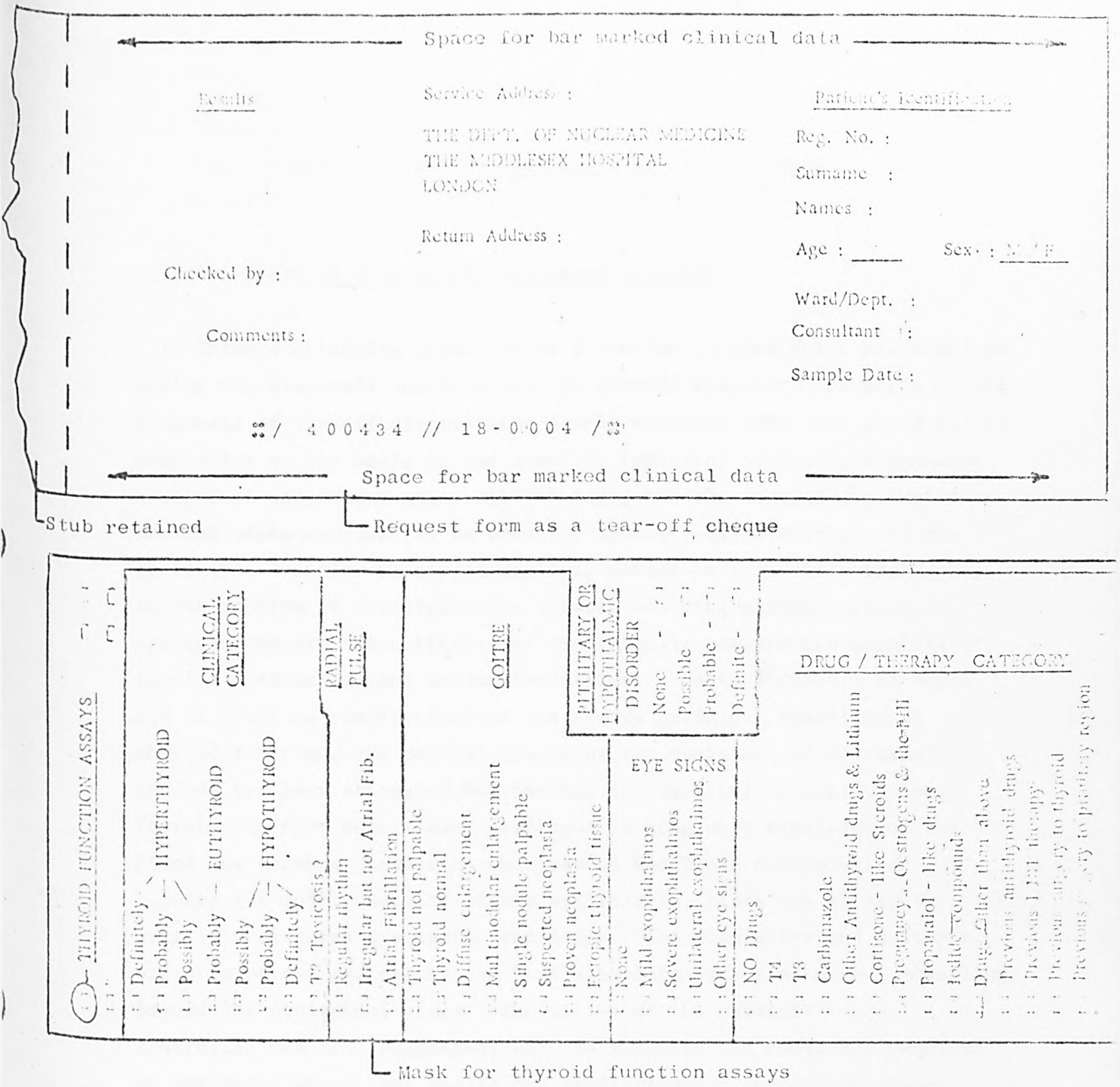


Masks in position over cheques

Cheques folded to input patient I. D. on three parts of form at once

Possible version of Supraregional Assay Service Request Form

Figure 3.16



Layout of mask(bottom) and form (top) for S.A.S. requests
Mask is shown for thyroid group of tests (T4,T3,TSH)

Figure 3.17

CHAPTER 4

Selection of Thyroid Assays by Clinical Data

4.1 Previous Work on Thyroid Discrimination

Three overlapping areas can be discerned in work which has aimed at aiding the diagnosis and treatment of thyroid disorder. Attempts to aid diagnosis of thyroid disease with mainly clinical data have given way to evaluation on the basis of the steadily improving biochemical measures. A clinical assessment must still be made, but the routine estimation of patient state can usually be obtained from the biochemistry. In the third area decision theory is applied, direct or more often implicitly, to the problem of discriminating between evolving patient states. Applications are often trivial or theoretical, however the problems of complex interactive and subjective criteria remain difficult to model and in practice simplifications are always assumed. Modelling of thyroid function, the medical system or the operation of the assay service has been attempted but has had little clinical application. Thyroid function models have developed in step with knowledge of the gland and hormone regulation, but beyond the basic conceptual or qualitative model there is little application, since the clinically available measures are sparse and noisy. The complexity and multiple criteria of the medical system have also largely defied useful modelling beyond the conceptual stage. The notion of the physician as a controller has been suggested, but the measures and knowledge required to use detailed patient models for prediction and control decision-making have had little practical impact. Exceptions to this are largely confined to acute care where patients are intensively monitored.

Precise assays of the plasma thyroid hormone concentrations were introduced in the 1970s. Earlier, diagnosis of thyroid disease and dysfunction had relied largely upon the clinical assessment of a large number of signs and symptoms. Various algorithms were applied to aid the discrimination of thyroid function (hyper- hypo- or euthyroid) or the particular disease (Graves disease, Hashimoto's syndrome, etc.). The aims were to assist the physician and improve the accuracy of classification by extracting the greatest possible information for some

group or sequence of observations shown to be optimal for this purpose. The observations, which varied between authors, were drawn from those considered important by clinicians. A sample of patients selected on some basis would be assigned to a class by experienced physicians after extensive testing and/or treatment. The initial, largely clinical, observations would then be examined for their ability to classify these patients, usually after "training" the algorithm on this or another patient set. The techniques employed will be discussed in detail in chapter 5 but usually Bayes or maximum likelihood approaches were used to obtain the probability of each class given a particular set of signs, the probability being derived from the incidence of these signs with each disorder class in the training data. Prediction was confined to estimates of the current patient state derived, with the exception of some observations. Success was defined as the ability to classify "well" the set of test patients, though a direct comparison with the performance of unaided physicians on these signs was often omitted. The published algorithms or indices normally claimed moderate successes, though they were rarely better than experienced physicians and few have found general exceptance. The arrival of cheaper and more precise hormone measures reduced clinical interest further. The clinician probably found the predictions little better than his own at the cost of a greater clerical load, and the less experienced physicians could not afford to dedicate the time and effort to obtain the consistenty in assesment needed in a specialised area. Input of the clinical data, sometimes duplicating medical records, was tedious and prone to individual variation. Computing the index or probability either took time or required resources including a computer and programming effort and furthermore those patients giving clinical doubt were often classified with uncertainty too. If these algrithms are to be routinely applied they, like any test, must show either reduced costs - which is impossible since application always involves additional effort - or a better discrimination to improve patient management. This has rarely been convincingly shown and some authors have justified the process as an attempt to locate an "optimal" subset of signs. The algorithm itself must show benefits before it will be used reglarly with these signs and in practice this "optimal" set has not been identified. The variation between studies is, no doubt, partly responsible, but more importantly the biochemical tests included have changed, steadily becoming of increasing importance. Computers were soon applied to the problem of

data handling and calculation but while more data and greater algorithmic complexity could be accommodated, problems and costs with hardware, software, or interaction were introduced without significantly reducing other costs or making the overall system acceptable within the medical environment.

Of the algorithms for discriminating thyroid function only the Crooks/Wayne indices for hyperthyroidism have achieved any significant application in routine observation at a number of centres (in the U.K.). Even so the improvement in assays and the continuing problems of technical variance mean that the indices are now largely confined to patient studies serving as a convenient and comparatively well defined synopsis of clinical condition. The index is obtained by a simple totting up of weights assigned to the presence of each clinical sign or symptom on a standard form; the weights being defined from incidence data in the patient samples of the original studies (actually derived from the log ratio of relative incidences). Apart from the continued use of these indices, there clearly remains a need to assess precisely a patient's clinical condition. Although biochemical measures are tending to redefine thyroid dysfunction and disease, the biochemical abnormalities must be shown to have consequences for the present or future clinical state before intervention can be justified.

Thyroid disease, as distinct from dysfunction of thyroid hormone regulation, is more difficult to diagnose and the sensitivity of the clinician to malignant disorders is important. Once clinical suspicion has centred upon the thyroid gland, however, the relevant biochemical measures have again considerably improved. Dynamic hormone tests, antibody determinations and scanning techniques are probably now more satisfactory for the resolution of clinical suspicion than any attempt at discrimination centred round the clinical data. There remains the role of selecting patients for these tests which, while relying upon the physician's overall judgement, may be assisted by attempts to quantify the relationships between clinical signs and these tests. Fragu et al (1974), for example reported that there were no abnormal scans of patients with a normal thyroid palpation which suggests, assuming a consistant population, that the scan is uniformative for these patients.

A major weakness of the discriminant approach to diagnosis of

thyroid function lies in the definition of the discrete states, or 'final diagnosis'. Firstly the basic assumption of a distinct state seems incorrect. Hyperthyroidism often shows both a gradual onset and (historically) in some patients, a slow remission of clinical signs. This suggests that however accurate the measures of the underlying state may become, an unequivocal statement on therapy may not be possible. Secondly the difficulties and differences between studies in defining and confirming the "final diagnosis" for the patient sample involved have limited their usefulness and comparability. Final diagnosis is usually stated as being based upon the evaluation of extensive diagnostic and treatment criteria, which are rarely specified in detail, particularly important in the classification of borderline cases. The technique is retrospective as the physician's final decision as to the patient's state includes the initial observations used by the algorithm to reclassify these patients. This process of obtaining final diagnosis is impracticable on a routine basis so the established classifiers are limited by the large number of signs and the comparatively small data-base that can be established. Studies which employ samples of distinct populations for euthyroid and abnormal classes, or those which allow the data-base to be updated by "easily established" diagnosis, obviously tend to be biased by the lack of intermediate and "difficult" cases. Sandel and Vorgt (1978) examined, as is now common, a largely biochemical data-base and took an approach based upon cluster analysis. In a measurement space defined by four routine thyroid hormone measures (T4, T3, basal TSH, and TSH after TRH) they claim to have identified five distinct clusters which do not relate in a direct manner to the clinical states used to describe these patients. This approach is suitable for routine data accumulation if these clusters relate to distinct responses to treatment which are suitably related to the patient's clinical condition.

A failure to examine the response to therapy as the basis for clinically useful diagnosis is common in much work on discrimination. Decision criteria have in some cases included test costs and an attempt to evaluate relative risks of misdiagnosis but this had not extended to a detailed examination of therapy costs or to establishing distinct patterns of patient behaviour. In practice the expected response to treatment is the basis for the medical decision actually made, as distinct from any of the finer points of diagnosis. It is possible to

follow, from routine biochemical tests, the changes over a time with therapy which can then be used to describe and distinguish patients. At the simplest, individuals can be classified by the final treatment applied. This would allow a large data-base to be accumulated without excessive cost.

A problem with this 'therapy-based' classification is the possibility that a circular confirmation of diagnosis and treatement is being proposed. An uncertain or borderline case might continue to receive therapy unnecessarily because of the initial diagnosis and so "confirm" the original error. The assumption is that treatment will only continue if an improvement is observed which is maintained. If the improvement is slight or appears transient then the physician should test by a trial cessation of therapy. It perhaps would be advisable to make explicit the region of uncertainty in which physicans may "experimentally" assign treatment randomly or on more general clinical suspicion. It should be recalled that while a large data-base may allow many inter-related or subtle aspects of the data-base to be elucidated, uncertainty cannot completely be removed. The large number of unrecorded clinical factors can be expected to introduce an effectively random input to individual therapy decisions which can continuously check the established decision ranges against drift or errors in the measures available.

The simple discrete classification of patients can be made progressively more detailed until comprehensive time-series models of the individual, finally limited by the frequency and extent of the measures, describe the patient in terms of parameters. In this way the discrete state would be replaced by an estimate of mean and confidence limits for the patient model parameters which can then be used to optimise test and treatment sequences aimed to produce some target state. This does not deal with patient costs or benefits, and whether the target state, (which is presumably nearer the population "norm") will be or is better for the patient is a decision for physician and patient to make. Several workers have considered testing and treatment costs, particularly Edwards (1970), but generally these are theoretical studies with trivial applications and costings and the decision theory associated is usually implicit in the reduction of the problem to a minimisation of uncertainty irrospective of testing costs, or a

minimisation of tests with some uncertainty constraint. Attempts to model the medical environment or even quite limited aspects of the physician/patient relationship which include realistic costings and which can be optimised are often premature. At the same time it is necessary to be able to evaluate the merits of the different discriminators and algorithms used against the existing procedures.

A similar problem of evaluating a novel procedure continually occurs as new tests appear. That these evaluations have not always been sufficiently stringent is clear from criticism of a number of new tests by Inglefinger (1976), Holland and Whitehead (1974). These authors agree upon the need for more rigorous and controlled trials of such tests proposing a criterion which is essentially the discriminative ability of the test on the population to be routinely examined, together with a comparative examination of the economics and acceptability of the new procedure against the existing alternatives. This simple, rigorous procedure for the evaluation of a test can be applied to a discriminator or any algorithm for aiding test selection or interpretation. The emphasis on careful selection and definition of patient sample and the need for acceptability of the procedure is close to the criticisms already made of most medical applications of discrimination techniques. Three criteria emerge from this analysis. Discriminative ability and costs can fairly objectively be ascertained but the "acceptability" of the test may in some cases be more difficult to determine. The authors point out the need for any test to be capable of being used under routine conditions by personel unconnected with its development. This factor is particularly important as, apart from the rather subjective aspects of acceptability, procedures are often found to be less accurate or more expensive out of the hands of their originators. This approach seems to provide a suitable framework for the assessment of aids to medical decision-making in general.

A decision on the overall value of any new test or procedure then becomes an assessment of these three criteria. The physician must determine whether improvements in diagnostic ability are worth any increase in cost or decrease in ease of use. Obviously a test showing real improvement in all features is acceptable. If the algorithms for discrimination of thyroid function are examined in this way it is clear that apart from general acceptability, the inevitably higher costs must

be earned by improved diagnosis when compared with the unaided physician.

In the study of Fragu et al (1974), when an index of clinical state was included with two T4 tests, a T3 and a FT4I test to discriminate hyperthyroidism, the assays proved the most powerful discriminators. This is typical of modern work in which the clinical data have taken a secondary place to a biochemical resolution of patients put forward for testing by clinical suspicion. A considerable number of tests and procedures have appeared and in their turn been superseded. As described earlier, the current routine measures are assays of basal T4, T3 and TSH. The thyroid hormone measures (T4, T3) can be extended to an FTI, a free- thyroid (T4 or T3) index, by the additional estimation of protein binding capacity and the TSH test can be applied to a simple dynamic test, the TRH response test. This requires several TSH measures for basal 20 minute and 60 minute TSH concentrations after an injection of TRH. Much current work is centred about the improvement and the evaluation of these tests individually or in combinations for thyroid diagnosis.

In clinical practice there is an increasing tendency to use these tests to confirm even the least doubtful diagnosis. The test result is also useful to supply a "benchmark" against which the subsequent therapy may be assessed. In the paper by Fragu et al (1974) where an index of clinical state was included with the tests, the clinical diagnosis either by physician or 'computer' was correct in some 80 - 90 % of cases. Clearly there is a percentage of presenting cases which require discrimination, or confirmation of their borderline status, perhaps by a number of tests but uncertainty can still arise here because of assay measurement noise and the difficulty of interpretation of equivocal results. A majority of those tested are probably euthyroid so a significant proportion of the 'abnormal' results are in fact generated by these patients. The consequence is further testing, confusion and delay. Physicians tend to try to short- circuit this process by ordering a number of tests simultaneously, producing the well established near exponential growth in assay requests. It seems equally certain that this is not accompanied by an equivalent growth in the information derived by the physicians. Against this background Britton et al (1975) began to examine the selection and interpretation of

thyroid assays. A strategy was proposed to allow the assay service to interpret assay results through decision ranges, for the immediate selection of further assays. In this way unnecessary tests are avoided.

4.2. Definition of Assay Decision-Ranges

Assuming discrete patient states, a maximum likelihood approach would be to assign any observation to the most probable state. For clinical purposes however, a clear statement of the ambiguity of the result is more useful. Britton et al (1975) therefore defined borderline regions between those regions where a result could be considered "definite". These decision ranges were used to establish a strategy for selection of the routine T4, T3 and TSH assays. The aim was to eliminate unnecessary tests by limiting each request to a single screening test unless the result of that test was borderline, in which case a second test would follow automatically.

The definition of these decision ranges was based upon the assay distributions of patients routinely tested for thyroid function and assessed as clinically euthyroid. It was assumed that the T4 and T3 distributions for euthyroids were approximately Gaussian and the boundaries derived from the probabilities associated with a fit of this distribution to the data. These boundaries were then checked by searching for incorrectly assigned results and the boundaries modified to reduce misclassification. TSH results do not fit a single distribution but a similar procedure was followed based, however, more upon the observed incidence and the subsequent check of successful classification. As might be expected the amplified error signal from the pituitary (TSH) is potentially the most useful measure but the lack of precision in the low dosage region effectively limits single basal measures to determination of hypothyroid patients, who may be uncertain after the T4 and T3 tests . The T3 test, though required to distinguish T3 toxicosis, was not much more successful than the T4 test with which it is strongly correlated. Pain and Duncan (1976) took a similar but more rigorous approach to establishing three distinct sub-samples (hyper- hypo- and euthyroid) from a routine population, validated by extensive testing, to define three distributions. These observed distributions were then used to define regions of overlapping results as

borderline regions. This is a more accurate procedure but introduces the need for well established final diagnosis. Survey data from Evered et al (1978) have confirmed the Gaussian T4 and T3 distributions in a normal survey population, but neither procedure is ideal and a definition based on long-term therapy response might be better. The upper part of figure 4.1 shows the decision regions for a single T4 test against the probability distributions of actual results derived from the study by Britton et al (1975).

An alternative to the decision statement is the probability of a particular result. Raw probabilities are often difficult for the physician to relate to outcomes but the combination of clear decision ranges augmented by the "odds" of such a result from a euthyroid individual would give sufficient information to evaluate a particular result.

4.3 Assay Precision

Patient plasma samples are measured in batches and the outcomes checked by replicates for each sample and inclusion of a number of quality control "standards". These standards are drawn from a large pool of unused serum. As independently derived standards are not available and the plasma pool is finite, assay precision and accuracy must be confirmed by checks on patient and normal populations. Routine quality control can, however, indicate random and procedural errors within and, to some extent, between assays and laboratories. This is usually sufficient to guard against longer-term drifting of reults.

Given blood drawn from euthyroids, three causes of variance in the results obtained can be expected to arise from:

(i) Individual variation, distributed randomly through the population or associated with age,sex etc.

(ii) Within assay variation from random fluctuations in a single assay procedure, perhaps through poor repeatability in an instrument.

(iii) Between assay variation arising over time, between operators or laboratories through random or systematic differences in procedure.

The within assay variance is not constant over the measured range, as figure 4.2 shows for the three routine thyroid assays. Assay procedures can be optimised to reduce overall error, or to some extent, move the region of minimum error over the measured range. It is usual to centralise the minimum error about the "normal" range to assist discrimination of normal and abnormal individuals. If, however, the borderline region is the only, or most important region for observation then it might be possible to usefully relocate the region of minimal error. Limitations in the detection of very small hormone concentrations mean that the T3 and, particularly, the TSH tests tend to have lower precision in the low borderline range (see figure 4.2 again) and to be more useful in the higher ranges. This arises partly from assay limitations and partly because of the changes seen in abnormal physiology. As described in chapter 2 the appearance of hyperthyroidism is accompanied by a relative increase of T3 over T4 in glandular content and secretion. Indeed, some cases show little or no increase in T4 (T3-toxicosis). T3 testing is therefore particularly helpful with these patients. In hypothyroid patients the gland attempts to maintain output of the physiologically important T3 so there may be little change in T3 levels as the TSH levels rise swiftly to stimulate the declining glandular output. It is possible to make limited modifications to the T3 and TSH assays to improve precision in the most useful borderline high range. The T4 test can then be employed for an initial screening of all patients optimised for precision about the normal range. The system is outlined in the lower half of figure 4.1.

4.4 Assay Selection Strategies

The study by Britton et al (1975) confirmed that the strategy outlined above, using the T4 test for screening followed by either a T3 or TSH test as indicated by the T4 result, was acceptable and made sigificant savings in tests. The indication for a secondary test was a T4 result in the relevent borderline region. In effect the strategy has two stages, though it is possible to "recycle" and repeat assays after

what appears to be an erroneous result. The two stages correspond to an initial or screening test and an optional secondary test. Three decision points are implied by this procedure (see lower half of figure 4.1 again). The first decision is the selection of the screeing test. This will always be a T4 assay since the majority of requests produce normal results because at this point patients on therapy were excluded from the strategy. The effects of therapy on the classification of these patients is important as in many cases the physician may be more concerned with changes or possible trends over time. At the second decision point the initial assay result (a T4 assay) is examined and on the basis of the result a secondary test may be selected. It is possible at this point, or after the secondary test result, to repeat an assay if an error is suspected. In most cases the whole process is simply an immediate T4 test followed for some patients by the secondary test. The T4 test result is usually supplied as soon as it is available. A clinical statement may be supplied with the request and any severe discrepancy with the assay result could call for further testing. This was left largely to the judgement of the biochemist checking results as the clinical data were insufficiently detailed or complete to quantify its effects.

The aim of the strategy was to supply minimal data necessary to achieve a satisfactory discrimination and for this purpose the secondary tests were considered "better" for some patients and examined independently of the T4 result. There are strong correlations between these results, however, which means a loss of information if ignored. Figures 2.4 and 2.5 shows the changes of T4, T3 and TSH which can be expected in the known disorders of thyroid regulation. A pair of results falling outside the expected regions implies an error and the need for further testing. At least it would be useful to present the results together when the physician could then decide if further testing was required.

A more important weakness of the strategy is the lack of input from the physician or patient and the exclusion of the large number of patients on therapy. If the physician is to accept assay selection by the sevice, it must ensure that clinical doubt is as fully resolved as the physician could have obtained with freedom to choose as he wished.

Though the picture remains confused, a number of investigators have found changes in thyroid hormone levels with age or sex and between ambulatory and resting patients. These factors could have an effect upon the decision ranges for different patient sub-populations. Thyroid therapy clearly has modifying effects upon thyroid measures. Although time-dependant factors may be of importance in the selection of tests, many of these patients are in fairly stable equilibrium over the long term and a simple determination of the success of hormone regulation would be satisfactory. The inclusion of therapy effects, and hence those patients, into the strategy therefore seems possible.

The changes outlined above modify the input to strategy decisions but do not alter the rationale for the selection of tests. The basic assumption is that the screening test (T4) result alone will normally be adequate and the secondary tests simply resolve residual uncertainty, whether this arises form the screening result alone or in combination with the clinical statement. There are occasions where T3 or TSH data are important irrespective of the T4 result. To resolve these considerations fully would require a more detailed model of thyroid regulation but it is possible to consider the value of simple modifications to the strategy. A TSH result for patients clearly hypothyroid by the T4 assay differentiates between primary (thyroidal) and secondary (pituitary) hypothyroidism. While this may not affect therapy it would serve as a benchmark against which subsequent TSH results could be assessed. The TSH results appearing after a borderline low T4 result in secondary hypothyroid patients treated with T4 might be confusing without the initial low TSH result for example. A number of simple modifications are considered which allow greater flexibility in output response.

4.5 Alternative strategies and the assessment of their performance

The strategy devised by Britton et al (1975) which generates a secondary test only after an equivocal screening test, whether including clinical data or not, is taken as strategy 1. An extension of this allows a secondary test for equivocal or clearly abnormal results. This strategy (2) will continue to save secondary assays because of the large number of normal screening results and provide an additional bench-mark

and check upon patients likely to be about to receive, or already on, therapy. It assumes that patients on therapy in the normal T4 range do not require a secondary test, though strong clinical doubt may relax the conditions. In some cases, however, such as T3 toxicosis or a delayed pitiutary response, it might be maintained that a T3 or TSH result is needed. Without time series data and a much more complex model of patient behaviour such requirements are difficult to include without ad hoc modifications. An alternative strategy (3) relying upon the clinical data supplied might combine some of the advantages of strategy 2 with the savings of strategy 1. In this strategy it is assumed that the abnormal cases are best confirmed by a T3 or TSH result while uncertain results require a combination or results. The aim is to select the screening test on the basis of the clinical data presented with the request. While this would combine diagnostic power and economy it relies upon the clinical data to distinguish patients and may not provide an intital T4 result before therapy. The T4 result is the most likely routine test so physicians will have to follow a transition between tests, though there will be considerable overlap as the patient moves through the uncertain regions of both tests.

The above strategies have emphasised the two most important stages in testing but not described actions in the event of continuing uncertainty even after both results are available. Subsequent actions depend upon the assessment of the likelihood of assay error and importance of resolving patient state. These cases are difficult to include systematically and could be considered to represent the limit of discrimination by routine tests. Apart from repeating the basal tests, dynamic measures might be required, though it is important to distinguish between results which seem to indicate assay error and those which suggest a truly intermediate state.

As described below, it was decided to collect a data-base of routine thyroid assays, including clinical data which can be used to assist the interpretation and selection of these assays. The effect of clinical data at the two decison points can then be examined for each strategy and strategies compared with routine assay selection by requesting physicians. It is important to emphasise that the aim is to maintain an output which can be used by physicians at minimum cost, not

the replacement of the physician's function by 'automatic' discrimination of patient state.

The clinical data can be applied at each decision point to estimate the patient state and hence the assays required, and to check for discrepencies between clinical and biochemical measures. The value of the clinical estimate depends upon the particular strategy and costs, but the aims at each stage are similar. At the first decision point the clinical data can be used to update the prior probability of a normal result. To have any effect upon strategy 1 a cost must be attached to the delay before an uncertain T4 result is followed by a secondary test and the data must be able to predict T4 results in the correct borderline region. Predicting patients in this state would seem to be difficult, without past test results, unless particular clinical signs are especially good at discerning clinical uncertainty which is reflected in the underlying patient state. This condition is relaxed somewhat for strategy 2 where any abnormal T4 result requires a secondary result, while strategy 3 relies upon clinical discrimination to select the secondary tests at once. At stage 2 the screening test can be assessed by the clinical data. Confirmatory clinical assessments will effectively narrow the borderrline region while discrepancies will tend to widen them.

To test these strategies it is necessary to accumulate a data base of routine requests from physicians, the test results and clinical data. The collection of such data must be acceptable to physician and assay service and show significant returns in terms of reduced costs or improved output in return for any extra effort by the users. The clinical data must indicate clinical uncertainty rather than discriminate the state of thyroid function. To assertain the acceptability of this type of data collection a pilot study was undertaken with a firm of physicians headed by Dr. J. Nabarro, to collect additional clinical data with each thyroid assay request. For this purpose a new form was designed for assay requests which included a number of specific clinical signs.

4.6 The Selection of Clinical Data

As noted earlier, previous workers have attempted to establish a distinct group of clinical signs which would be particularly effective in the discrimination of the state of a patients thyroid function. A number of papers were scanned for the most useful signs for hyper- and hypothroidism. Results given in various ways (weights or relative frequency ratios) were drawn from the incidences of variable sets of signs in different patient populations. The authors usually assumed independence among the signs included. The papers from Crooks et al (1959) and Billewicz et al (1969) cover the Wayne indicies. Oddie et al (1972) presented data from a number of papers and from their own sample. Gustafson et al (1971) reported on a comparison between the actual and the subjective estimates of clinical incidences. The actual rates from the sample obtained were normally reported. Some care is needed in interpretation since apart from different samples there are variations in the definition and recording of some signs. An example is the exclusion of thyroid goitre and bruit observations by Gustafson et al (1971). Some signs might reasonably be expected to show correlation, hyperkinesis and fine finger tremor for example. Billewicz et al (1969) stated that an overall rate of nearly 30 % was observed for partial or complete disagreement between clinicians. There appearto be differences in the discrinating power of the individual signs according to the author quoted. There was little information on the uncertainty in clinical judgement associated with each sign. An important aim of this work was stated to be the reduction of clinical uncertainty and establishing the relationships between the particular clinical observations, their uncdertainty and the underlying biochemistry would probably be more useful than another attempt at automatic diagnosis. Clinical uncertainty is of particular importance for test selection. Finally most of the papers included were restricted to patients who had not yet received therapy.

In practice the major constraint on the selection of clinical signs arises from the clerical effort of the physician in recording them and hence from the method used to transfer the data to the assay service. It may be reasonable to go through the detailed and structured questionnaire typified by that employed in the Wayne indices when

biochemical measures are unavailable or a study is in progress, but a normal consultation neither allows the time nor requires the precision of such a procedure. Indeed it could be argued that in practice the various algorithms simply transfered the problem of evaluating a set of signs to that of deciding whether the individual signs are present. Any clinical data would ideally be easy to obtain and supply and clearly understood. Quantitative clinical measures such as basal metabolic rate (BMR) or ankle jerk times are lengthy and require special equipment. Ideally to minimise the number of signs each should be capable of indicating both hyper and hypothyroidism. "Physical movement" might be a suitable example, with "hyperkinesis" and "slowness" as the alternatives to normality. There should be freedom to indicate uncertainty in assessment. As the final selection of the signs is heavily dependent upon the method of data collection it is described in the next section.

4.7 Form Design for the Pilot Study

To allow data collection with the minimum disruption of the existing system, the routine request form was modified for the pilot study. No other methods of data collection were practicable given the limitations of cost and acceptability. Requirements for the form were:-

i) Easy input/output.Physicians must use the service and must find the form quick and convenient to use.Handwritten input was therefore minimised, the ticked boxes could also be made machine readable to reduce service effort.

ii)Content must include the information and be compatable with the existing hospital form.

iii) The form must be physically easy to use and store by the service and in the medical record.

As the existing system had specified a separate form for each assay request and the physicians using the pilot study form were exempted from the strategy they would have had to duplicate requests for each assay. This was avoided by specifying a form with three coloured "flimsy" tear-off layers, one for each assay and a backing sheet. The "flimsies" are returned with the appropriate results while the backing sheet can be retained for pilot study records.

To minimise clerical effort and take advantage of the physician's ability to integrate the whole range of impressions ranging from changes in specific signs to the patient's subjective self-assessment, it was decided to request an overall clinical assessment. Variations in the strength of suspicion are allowed by a range of confidence for each disorder expressed as "possible, probable and definite". A number of individual clinical signs were considered but it was thought that each observation would have contributed to the overall assessment and that they would therefore lose their predictive value. It might be argued that drawing the physician's attention to a particular sign would tend to ensure agreement between that observation and his general view of the patient. A sign probably less sensitive to subjective bias, and fairly easy to obtain, was the patient's pulse rate, but again even the minor structure imposed by such a regular measure was thought likely to reduce the habit of compliance by the physician. It was agreed that some distinctions based on signs indicating the possible underlying thyroid disorder might be useful to distinguish sub-populations of patients. The presence and status of goitre and eye signs would be indications of hyperthyroidism, but would also identify distinct groups which it was hoped would show different responses (though time-series data might be necessary to obtain meaningful results). The determination of thyroid antibodies was common for these patients and though it may correlate with goitre or eye signs was thought to be more often obtained with borderline patients. Pituitary disorders, though relatively uncommon, could give rise to confusion over TSH results through secondary (pituitary) hypothyroidism. Finally the present and previous treatments of the patient were obtained as far as was considered relevent to thyroid disorder.

The final design of the form used in the pilot study is shown in figure 4.3. The need for compatiblity with the standard hospital form determined the patient indentification and some other aspects of layout and size. In the pilot study operation, the form would be returned with the results in the lower right-hand region. This means that the form could be gummed in overlapping sequence into the medical record, the result and treatment at that point being visible at a glance as shown in figure 4.4.

4.8 Data Collection

In an enhanced operation a single request would generate as many routine thyroid tests as required for each sample and the data from the request form would be used to create the current work records and work sheets. These would be updated by results and archived when testing was complete. The archived records would generate a new synopsis of the patient thyroid status including the present and previous assay results with any clinical and treatment data. For the pilot study the new forms were processed just as normal requests from other sources except that the new forms did not have to be duplicated for strategy requests and the backing copy was returned for subsequent analysis. Data from these backing copies of the request forms were transferred via coding sheets to cards and hence to tape and disk on-line files.

The patients were all seen routinely by Dr. J. Nabarro over a period of approximately six months. Some 669 records were accumulated on these patients for analysis (J.N.Data). In addition Dr. K. E. Britton made available the data obtained for the study which developed the original strategy and decision ranges. These data were obtained from requests from the hospital population over about fourteen months and consisted of 1,130 records. These clinical data were much less reliable and complete, being confined to a brief handwritten comment upon therapy and condition, together with general information on age, sex and source of request (physician, ward) drawn from the normal request form. Records contributed by J. N. in this KEB study could be identified and used for comparison with the current study. The variables included are shown in figure 4.5. The patient identification was removed from these data before further analysis. With both studies confidentiality was maintained by the physical separation of the encoded patient identification from the rest of the record. These identification files were not kept on-line and were processed independently of the associated records, the only link being the record sequence. No programme or record names identified the source or type of data held which was formated as compactly as possible to mask data structure. Code books were also separated and physically isolated. It is unlikely that the data involved would be of interest or especially sensitive to observers beyond this study, but these measures are felt to

be good practice and necessary to avoid any possible embarrassment to personnel or patients when data processing must occur outside the hospital.

4.9 Data Analysis

The aim of analysis was to compare the physician's direct ordering of tests with the existing strategy and a number of alternatives which included an input from the clinical data. The physicians taking part in the pilot study were exempted from the strategy but towards the end of the period began to request the strategy for some patients. This tends to reduce slightly the apparent saving of T3 and TSH assays which would follow the use of the strategy.

The data do not have a "final diagnosis" since there are insufficient time series data to consider a definition by treatment as outlined in section 4.1, so the strategy and tests cannot be analysed by their discriminative ability. If a secondary test, T3 or TSH, had been given to all patients or assigned randomly to a proportion of patients then they could be used with confidence to assess the ability of the strategies to reduce unnecessary tests. Instead only results required by the physician appear in the data and it must be assumed that they are a representative sample of all secondary tests. The bias that would seem to be introduced by the physician's action can be expected to favour borderline results, and therefore limits the effects of the stategy. Only the screening T4 test was applied to all patients and the analysis therefore revolves about this measure. The tables of figure 4.6 show the dependence of the occurrence of a T3 or TSH result upon the T4 result. The T4 results are divided up into the decision ranges used. The relative frequency of secondary results increases after a borderline T4 result suggesting that the physicians tend to succeed in preselecting patients with uncertain T4 results for the request of secondary tests.

The analysis of strategy operation is derived from an examination of the existing assay results and the degree to which the strategies supply information for decision-making while eliminating unnecessary tests. This is based upon the notion of "errors" as discrepancies between the screening and subsequent tests which would <u>not</u> have been

identified by the strategy. This is similar to the assessment of any test by determination of the rate of "false" positive and negative results given by the test. In this case, however, it is the strategy which is being scrutinised, not the ability of the assays to discriminate the underlying patient state. The original strategy relies upon the T4 result alone to indicate a clear diagnosis or the need for further testing and occasions where a secondary test result (T3 or TSH) contadicts this, are the strategy "errors". The result may be meaningful, as in T3 - toxicosis or secondary hypothyroidism, or may be merely reflecting an inherent assay uncertainty, but in either case use of the strategy might obscure an important result. Figure 4.7 shows the division of T3 and T4 space up into a decision space. As the borderline regions are widened the number of secondary tests rises and the number of errors declines, but unless all patients receive a T3 test the possibility of T3-toxicosis cannot fully be removed. As approximately two years elapsed between the J.N. data collection and the previous study which set up the decision ranges on a different sample, it was decided to check the existing decision ranges. This was done by the same method as set out in Britton et al (1975) and is detailed in Chapter 6. The TSH/T4 boundaries were unaffected but the T4/T3 boundaries were slightly raised and the new values were used for further analysis. Figures 4.8 and 4.9 show the performance of strategy 1 with the K.E.B. data and the J.N. data using the original decision ranges. Figure 4.10 shows the effects of the new T4/T3 decision boundaries for strategy 1. The T4 TSH and T3 results are divided into their decision ranges and the number of secondary results obtained for these patients which would have occurred using the strategy can be obtained from the borderline results. The number of errors is available either as absolute occurrances or percentages of the secondary test results which fall in that T4 decision region. The savings are calculated as a percentage of the number of tests requested by the physician. Both samples are of patients who are receiving no therapy. The savings are significant 50 % of TSH results and about 70 % of the T3 results requested by the physician can be eliminated with a small increase in error. If, however, the strategy is directly extended to patients on therapy, there is a condiderable increase in the error rate, though savings continue at a high rate (figure 4.11) of about 55 %. The figure also shows how strategy 2 would perform on these data. The 'false'

positive results dissappear at the cost of a fall in savings of T3 assays to 16 % and TSH assays to 42 %.

4.10 Application of the Clinical data

The present concern is with the role of the clinical data in the second stage of each strategy, that is, after the T4 screening test result is available. The technique used is linear discrimination with the secondary test results classifying each case through their decision ranges. The Statistical Package for the Social Sciences (S.P.S.S.) has been used to generate the discriminant functions and classification data. Classification is checked by this package on the original data used to determine the discriminant functions and a further test was made using and unbiased 'leave one' out technique. This is described in Chapter 5 and together with the more detailed and easily available S.P.S.S. package results used in this section. Discriminators were developed seperately for T3 and TSH results to use the clinical and T4 data to predict the dcision range of the subsequent assay result.

Figure 4.12 shows the classification results and the significantly predictive variables for the 243 cases with T3 results. Apart from the T4 results and age, all variables were binary, indicating the presence or absence of that sign. Missing observations, particularly ages, were included by assuming the mean or modal values. Re-classification of patients was 89 % sucessful with only three cases which would be classed as errors. The T4 result was the major discriminator, but apart from the clinical assessment, current therapy, goitre and eye signs made significant contributions. Figure 4.13 repeats the analysis for 205 cases with a TSH result again the T4 result, clinical assessments and current therapy have important predictive value. This time, however, age and the possiblity of pituitary disorder are prominent, though this partly arises from the lack of other indicators of hypothyroidism in the data base. The re-classification rate at 76 % is much lower than that obtained for T3 and since some 40 % of cases are missing data on age, the analysis was repeated on those 105 patients with known ages. On this smaller group the predictive variables were largely unchanged but a re-classification rate of 85 % was obtained. The TSH results also showed an increase in the error rate to 3 and 4 % of predictions but

this can be improved for cases with known ages. In practice many of these "erroneous" results are for either secondary hypothyroids or primary hypothyroids treated with T4 who have high TSH results. Whether they are insufficiently treated or showing a delay before pituitary output falls cannot be determined from the data.

The tables of figure 4.14 summarise the implications of this analysis for the strategies when applied to the whole range of patients. The very large savings obtained when the strategy is restricted to patients off therapy cannot be maintained with all patients even if clinical data is used. (The 75 % saving of TSH result must be viewed in the light of the increased error rate to reduce error rates of TSH assay savings must be traded away). Despite this, the clinical data can enable a significant reduction of secondary tests (30-50 %) to be obtained while ensuring that the remaining assays are sensitive to clinical doubt. This is maintained even if strategy 2 with its greater information for diagnosis and therapy is preferred. The preceding analysis has examined only the second decision point where the T4 result is available, and used expected savings and error rates as criteria to measure the benefit of the stategy operation against the physician's selection. It assumes that these results can be extrapolated to the whole sample. Before examining strategy operation and the value of clinical data at the first decision point a more complete examination of costs is required.

4.11 Costs of Strategy Operation

The savings discussed in the previous section are obtained mainly at the cost of introducing an extra lag before any of the secondary assays are reported. The delay means that medical records must be retained until the arrival of the final result and the patient cannot be assured that there wiil not be changes to the therapy or consultation date during this delay while the clinical 'impression' against which the assay result is to be judged has also faded. Introduction of the clinical data to the first decision on assay selection is an attempt to reduce this delay by simultaneous ordering of all necessary tests. As the rate of unnecessary secondary assays will increase with the inevitable errors in selection, so reduction in delay is traded for the

extra T3 and TSH assays. These additional tests will presumably arise from some degree of clinical suspicion and, despite a clearly contrary T4 result, it might be useful to have a confirmatory second result. Indeed a few cases in the pilot study with strong clinical suspicion but clearly normal T4 assay did show borderline or even abnormal secondary results which could perhaps be resolved by the physician. Reliance upon the T4 result alone for assessing the costs of these assays would mean that these contradictory occurances would be categorised as errors.

Assessment of each strategy requires a statement of possible actions and associated costs in the form of a loss function. Unfortunately some outcomes are difficult to evaluate. The cost of delay and/or the need for a repeated request may be uncertain as is the benefit of an automatically supplied result which merely confirmed a previous finding, revealed T3-toxicosis or differentiated the type of hypothyroidism. In figure 4.15 the possible actions at each decision point are given with an estimate of their relative costs for the three proposed strategies. The assays or combinations of assays are in the main, selected at two stages by each strategy before and after the initial test or tests have been performed. The three strategies cannot be directly compared since the information produced by the assay combinations is different and the cost of delayed results had not yet been included. Analysis must be centred about the T4 assay results because the secondary results are not always available and there is no other 'final diagnosis'. As the prior expectation is a normal T4 result, all strategies will require the T4 test at the first stage unless additional information from the clinical data suggests the likelihood of a borderline or abnormal result.

Probably the major factor in determining the respective strategy costs is the loss attached to any delay. If delay cost is ignored or set close to zero, there is no benefit in attempting to predict assay outcome from the clinical data. It will always be less expensive to wait until the T4 result is known to be abnormal or borderline before selecting a second test. The relationship between assay cost, delay cost and prediction rates is given for a single secondary test in figure 4.16. If the delay cost is half the assay cost, then for immediate selection of the second test, prediction of abnormality must be better

than 70 % to break even. In the rest of this section the delay cost had been taken to be equal to the basic assay cost.

The value of clinical data to each strategy is examined for the first stage of each strategy by examination of the T4 result available for each patient. As noted before this may mask some of the benefits of the clinical data, which can significantly improve each strategy selection of secondary tests, but has the advantage of being a fairly simple and conservative assessment. The discriminant analysis was repeated for five classes defined by the T4 decision ranges and part of the results are shown in figure 4.17 For all 665 patients re-classification was only 54 % successful which represents only a marginal improvement over the prior odds. Recalling the absence of 40 % of age records, those 381 cases with age and sex data were selected and the analysis repeated. The re-classification rate rose to 60 % with minor changes in the most significant clinical variables. As before, the clinical assessment and current therapy were important with smaller contribution from goitre, and eye signs. The detection of borderline low T4 results is particularly poor and reflects the lack of indicators for hypothyroidism within the data set. Clearly unless delay costs were considerable, there can be no benefit from clinical selection given the results of figure 4.17 for all patients. Instead the classification results for those patients with age and sex data are taken for further analysis.

The cost of each outcome, as defined by the five decision ranges, are given in figure 4.18 for the three stategies. Strategy 2 effectively reduces these ranges to three, euthyroid and abnormally high of low. The results of the discriminant ananlysis can now be applied directly to the loss function of figure 4.18. The cost and total number of secondary assays required are given for each strategy in figure 4.19. Only if strategy 2 is employed does the use of clinical data produce any reduction in costs and this marginal saving is obtained with a near doubling of the number of secondary tests. This result holds even if the patient sample is limited to those not on therapy, where the classification rises to 75 % largely through the increase of prior probabilities, leaving the relative contribution of the clinical data unchanged. When strategy 1 is employed the only gains arise from the

prediction of T4 results in the two borderline ranges. Given the continuous T4 distribution and the limited nature of the clinical data, the difficulty in isolating these regions is reflected in the high misclassification rate. Strategy 3 is more difficult to assess since the first test chosen maybe a T3 or TSH. For analysis it has been assumed that if the associated T4 result is borderline then the 'second' assay result is also likely to be uncertain and require another assay (a T4 in this case). There are disadvantages with this strategy for new patients or those on therapy and therefore it has not been considered further.

4.12 Conclusions

The two main aims of this chapter were to examine the practicability of collecting clinical data on thyroid patients and investigating the usefulness of these data in the selection and interpretation of the thyroid assays.

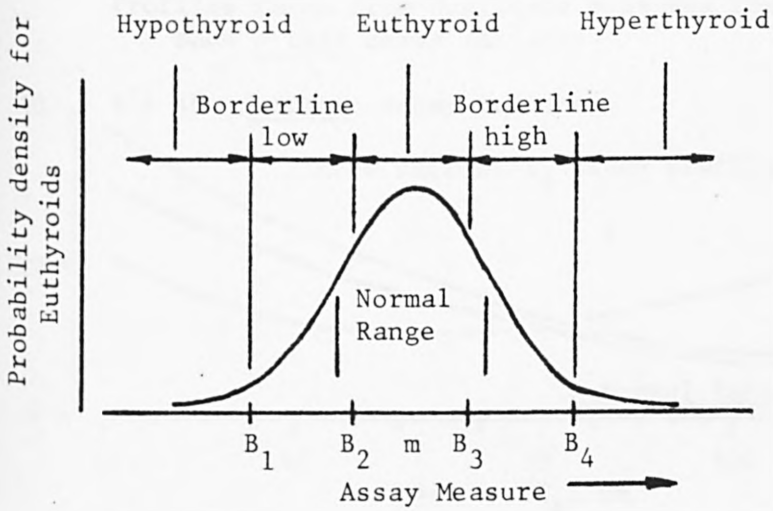
Experience with the request form and the particular clinical variables chosen for the pilot study suggests that they are generally acceptable for routine collection. The group of physicians using the request form maintained a response rate of 85 to 90 % for all variables, except age and sex, for the six months of the study. The physicians are continuing to use this request form with minor changes (figure 4.20) which should reduce the number of 'missing' goitre records. Hospital standardisation precludes alteration of patient identification so the handwritten age will probably continue to be poorly supplied. If the form is employed more widely, it is expected that response rates will fall. Nevertheless, ease of use, which this request form provides, and the knowledge that the input of accurate data enables the most useful return from the assay service, should ensure that the quality of the input data is maintained at an adequate level.

It has been shown that the original strategy can be used to eliminate a large proportion of secondary assays on a new sample of patients off therapy. If, however, the strategy is extended directly to all patients, there is a rise both in the proportion of T3 and TSH assays and the rate of biochemical 'contradictions' missed by the

strategy. The clinical data can largely restore the assay savings and reduce the error rate while directing secondary assays towards cases with clinical suspicion. The clinical data are less successful when applied to reduction of the delays introduced by the strategies by prediction of uncertain T4 results and unless delay costs are made large there appears to be little benefit. The effect is to shift the secondary assays to cases with clinical suspicion without significantly reducing their number. This may have the advantage of weighting clinical data heavily, against the T4 result, but produces a large number of unnecessary tests which themselves are open to random errors. Not considered here is the advantage of having two results at the second decision point.

Among the clinical signs collected, knowledge of the physicians opinion and the therapy status of the patient were as expected important indicators of the patient state as expressed in the assay results. The additional clinical data also made some contribution with eye signs and goitre status predicting T3 results and age and pituitary state predicting some TSH results. These dependencies examined have here been limited by the assumptions underlying the linear discriminator used.

Derivation of Decision Ranges and Assay Selection



Original decision boundaries from K.E.B. data on "euthyroids"

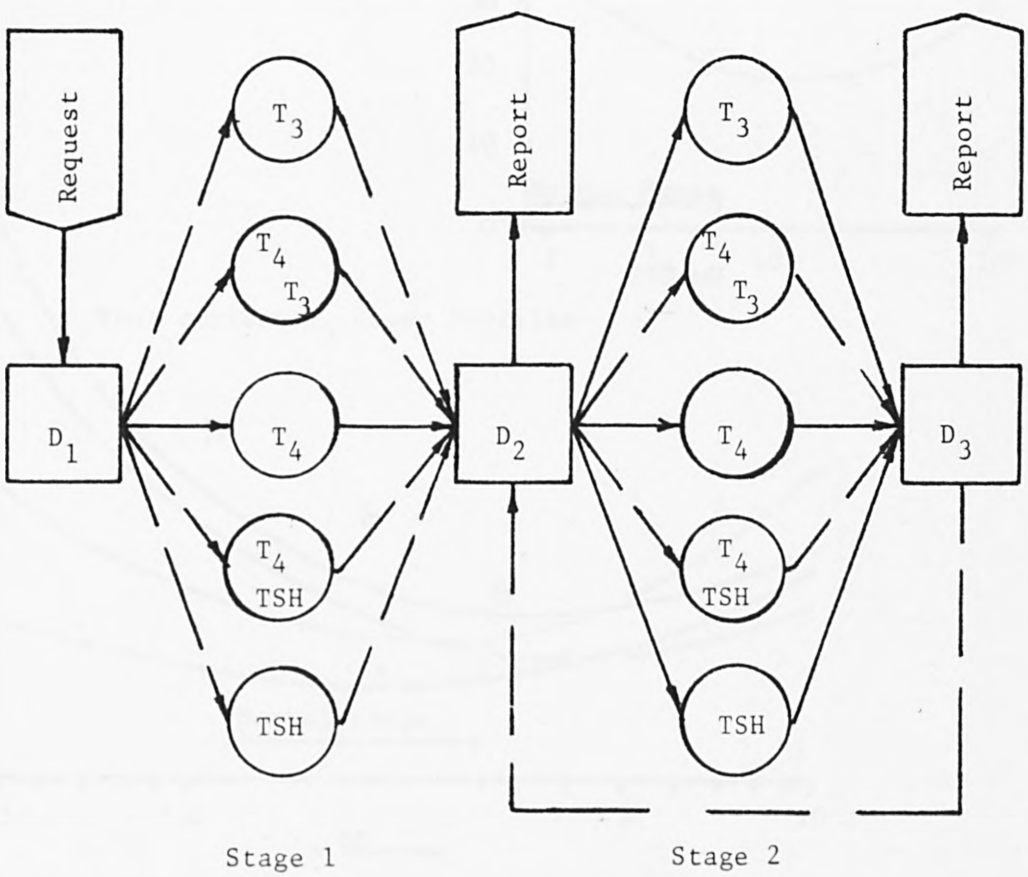
2% were > B_4 (176 nM)

29% were > B_3 (118 nM)

30% were < B_2 (77 nM)

7% were < B_1 (38 nM)

Sequence of Testing and Assay Selection



Decision ranges and assay selection sequence Figure 4.1

N.M. THYROID FUNCTION ASSAYS MIDDLESEX HOSPITAL DEPARTMENT OF NUCLEAR MEDICINE

Record PRESENT STATE. Mark ONE of each category

Clinical
0 ☐ Definitely
1 ☐ Probably – HYPO
2 ☐ Possibly
3 ☐ Probably – EUTHYROID
4 ☐ Possibly
5 ☐ Probably – HYPER
6 ☐ Definitely
7 ☐ T3 Toxicosis

Previous Therapy
0 ☐ None
1 ☐ Antithyroid drugs
2 ☐ 1 131 therapy
3 ☐ Surgery to thyroid
4 ☐ Surgery to pituitary

Thyroid Antibodies
0 ☐ Not known
1 ☐ Not present
2 ☐ Present

Eye Signs
0 ☐ None
1 ☐ Exophthalmos
2 ☐ Lid lag
3 ☐ Other signs

Goitre
0 ☐ Thyroid normal
1 ☐ Diffuse enlargement
2 ☐ Multinodular enlargement
3 ☐ Single nodule palpable
4 ☐ Proven neoplasia

Pituitary / Hypothalmic Disorder
0 ☐ None
1 ☐ Possible
2 ☐ Probable
3 ☐ Definite

All / Most features unchanged since last request on this type of form

No. .....

Surname
First Names
Date of Birth

Mr
Mrs
Miss

Ward / Dept. :

Consultant :

Return to :

Dates : Sample :
Received :
Report :

Assay Required :

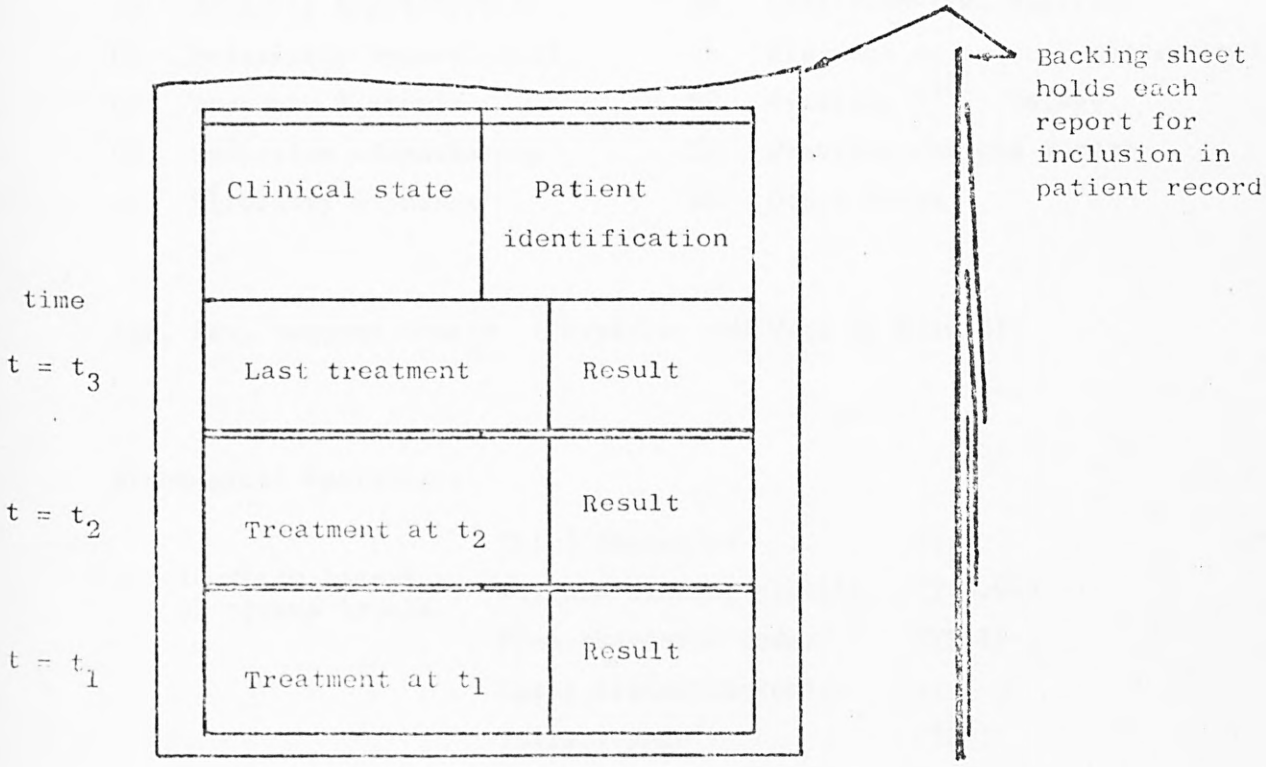
Any additional Clinical comments :

Present DRUG CATEGORY Mark ONE or MORE

0 ☐ None
1 ☐ T4
2 ☐ T3
3 ☐ CBZ , PTU.
4 ☐ Other antithyroid drugs & Lithium
5 ☐ Cortisone – like Seroids
6 ☐ Pregnancy, oestrogens and the Pill
7 ☐ Propranalol-like drugs
8 ☐ Iodide compounds
9 ☐ Any other drugs

ASSAY RESULT		COMMENTS
T4	nmol / L	
FT_4 I		
T3	nmol / L	
TSH	mU / L	

Request form used during pilot study to collect clinical data (J.N.D.) Figure 4.3



Request form may be stored in the medical record in an overlapping sequence to allow easy access to results and therapy Figure 4.4

Variables collected in the K.E.B. data

Clinical Variables:-

CØ	Definitely hypothyroid	DØ	Unknown/None
C1	Probably hypothyroid	D1	Thyroxine (T_4)
C2	Possibly hypothyroid	D2	Triiodothyronine (T_3)
C3	Probably euthyroid	D3	Carbimazole
C4	Possibly hyperthyroid	D4	Propylth. or perchlorate
C5	Probably hyperthyroid	D5	Cortisone-like steriods
C6	Definitely hyperthyroid	D6	Pregnant or an oral contraceptives
C7	Probably T_3-toxic	D7	Previous I^{131} therapy
C8	Endocrine exophthalmos	D8	Previous thyroid surgery
C9	Pituitary disorder	D9	Other drugs

Age, Sex, Request Source (Physician and Ward or Clinic)

Biochemical Variables:

In vitro Assays of plasma levels	Total thyroxine	(T_4)
	Thyroid-binding protein	(T.B.G.)
	Free thyroxine index	(FT_4I)
	Total triiodothyronine	(T_3)
	Thyrotrophin	(TSH)

The T.B.G. measure is an estimate based upon a "Resin T_3 Uptake Test" (RT_3U)

Varaibles included in the study by K.E.B. Figure 4.5

Dependence of Secondary Testing upon FT_4I Result

All Patients in the J.N. Study

Secondary Assay	FT_4I results divided into decision ranges				
	1	2	3	4	5
No T_3 Result	21 (84)	(67) 72	(187) 70	(95) 52	(52) 54
T_3 Result	(4) 16	(26) 28	(81) 30	(87) 48	(45) 46
No T.S.H.	(6) 24	(34) 37	(202) 75	(128) 70	(90) 93
T.S.H. Result	(19) 76	(59) 63	(66) 25	(54) 30	(7) 7

Patients without current therapy from J.N. Study

Secondary Assay	FT_4I results divided into decision ranges				
	1	2	3	4	5
No T_3 Result	(10) 91	(25) 78	(93) 74	(14) 30	(12) 48
T_3 Result	(1) 9	(7) 22	(32) 26	(32) 70	(13) 52
No. T.S.H.	(2) 18	(4) 13	(99) 79	(38) 82	(23) 92
T.S.H. Result	(9) 82	(28) 87	(26) 21	(8) 18	(2) 8

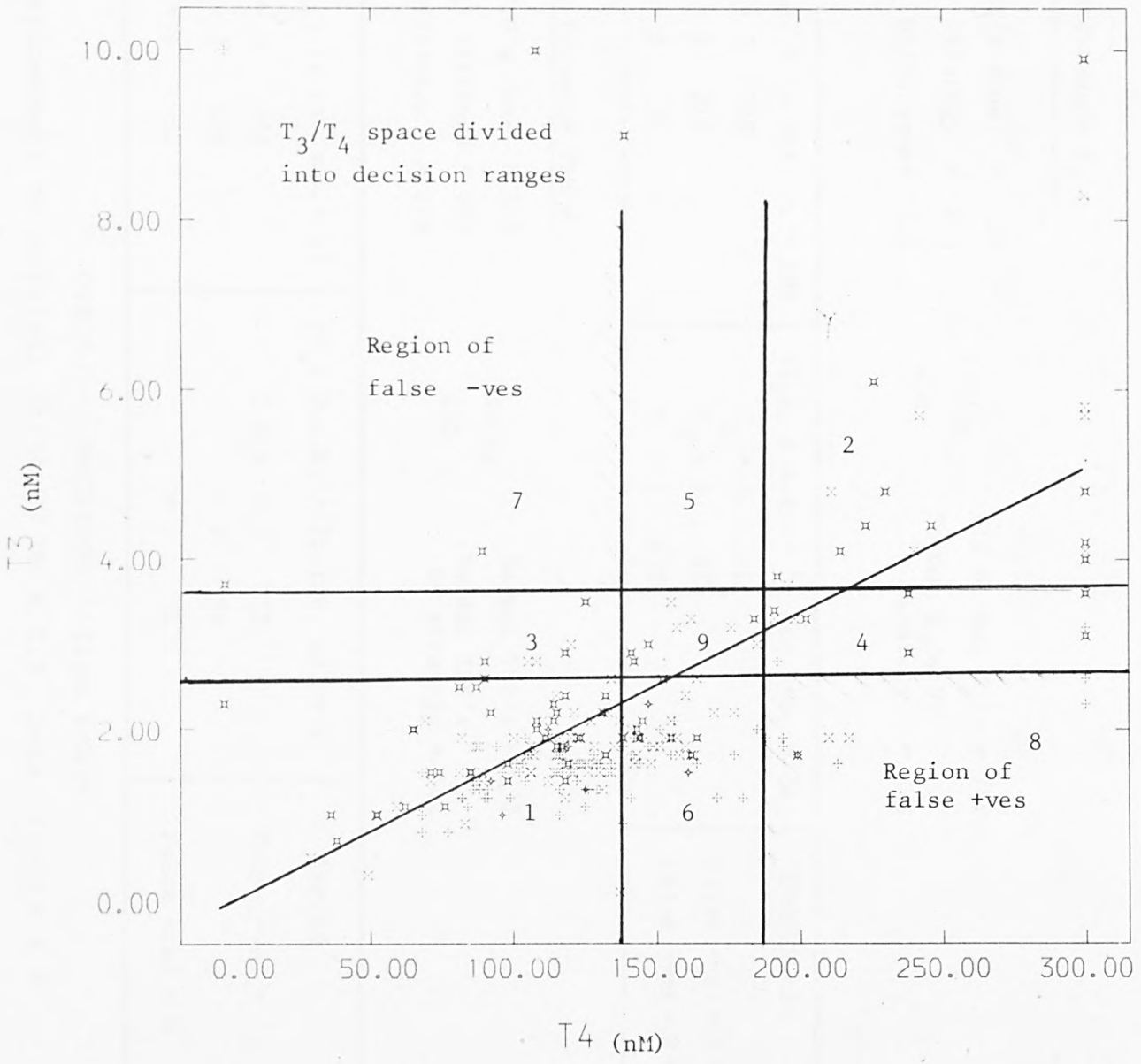
Each table shows the number of patients with and without a secondary test result (T_3 or TSH) according to the result of the FT_4I assay - figures in brackets. The unbracketed figures are the percentages, tested and untested, in each FT_4I decision range.

Tables show the dependence of T3 & TSH test requests upon the FT_4I result

Figure 4.6

Definition of "False" T_4 results as assessed by subsequent T_3 tests (from J.N. study)

Figure 4.7



SYMBOL	THERAPY
⁂	NONE
+	ON T4
¤	CBZ
✦	PREG

In regions 1 and 2 the T_4 test correctly classifies the patient as euthyroid or hyperthyroid respectively. Patients in regions 3 and 4 and 9 cannot be discriminated by the T_3 test and so remain uncertain while those in regions 5 and 6 receive a T_3 test. Patients in regions 7 and 8, however, are "wrongly" classified and have no T_3 test to check.

PREG - Pregnant

CBZ - Carbimazole

DS = 0, No therapy

K.E.B. Data
(0. File)

Assay Results by Decision-Aiding Ranges

	T.S.H.				FT_4I	T_3			
	1	2	3	u		u	3	4	5	
56	19	2	26	9	1	35	18	3	0	56
397	28	18	295	56	2	296	82	19	0	397
272	0	2	122	148	3	89	131	45	7	272
213	0	0	26	187	4	14	144	41	14	213
43	0	0	7	36	5	9	8	3	23	43
981	47	22	476	436		440	383	111	44	981

Strategy Performance T_3's

Total T_3's done = 538
T_3's by strategy = 213
Difference = 325

Saving
60%

71% Normal T_3's = 71%
Normal T_3's by strategy = 27%

FT_4I, D.A.R. = 4, tot. no. = 199	FT_4I, D.A.R. = 5; tot. no. = 34	ERRORS = 28
T_3 = 3 72%	T_3 = 3 24%	
T_3 = 4 21%	T_3 = 4 9%	False -ves = 7 = 4%
T_3 = 5 7%	T_3 = 5 67%	False +ves = 8 = 24%

Strategy Performance TSH's

Total TSH's done = 545
TSH's by strategy = 397
Difference = 148

Saving
26%

Normal TSH's = 87%
Normal TSH's by strategy = 54%

FT_4I D.A.R. = 1; tot. no. = 47	FT_4I D.A.R. = 2; tot. no. = 2	ERRORS
T.S.H. = 3 55%	T.S.H. = 3 87%	False -ves = 26
= 2 40%	= 2 5%	
= 1 40%	= 1 8%	False +ves = 0

D.A.R. - Decision aiding range

Performance of original strategy on K.E.B. Data Figure 4.8

D1 = 0; No therapy

J.N.Data

Assay Results by Decision-Aiding Ranges

N File

	T.S.H.				FT_4I	T_3				
	1	2	3	u		u	3	4	5	
11	8	0	2	1	1	10	1	0	0	11
37	5	5	22	5	2	29	8	0	0	37
121	0	1	21	99	3	89	30	2	0	121
48	0	1	7	40	4	14	30	4	0	48
25	0	0	2	23	5	11	1	1	7	25
242	37	7	54	168		150	70	13	6	242

Strategy Performance: T_3's

Total T_3's done = 89
Total T_3's by strategy = 58
Difference = 31

Saving 34%

Normal T_3's = 78%
Normal T_3's by strategy = 34%

FT_4I, D.A.R. = 4; total = 34	FT_4I; D.A.R. = 5; total = 1	ERRORS ≃ 7%
T_3 = 3 88%	T_3's = 3 7%	False -ves = 0
T_3 = 4 12%	T_3's = 4 50%	False +ves = 7%
T_3 = 5 0	T_3's = 5 43%	

Strategy Performance: T.S.H.

Total T.S.H.'s = 74
Total T.S.H.'s by strat. = 37
Difference = 37

Saving 50%

Normal T.S.H.'s = 73%
Normal T.S.H.'s by strat. = 30%

FT_4I, D.A.R. = 1; total = 10	FT_4I, D.A.R. = 2; total = 32	ERRORS ≃ 0
T.S.H. = 3 20%	T.S.H. = 3 69%	False -ves = 2
= 2 0%	= 2 15.5%	False +ves = 0
= 1 80%		

For these assays T_3's not discriminative
TSH needed for FT_4I = 2,1

Performance of original strategy on J.N.Data Figure 4.9

DS = D1 = 0, No Therapy

J.N./K.E.B.Data

Assay Results by Modified Decision Ranges for T_3

D.A.R.'s FT_4I 38 78 118 176

1 2 3 4 5

FT_4I	T_3				
	u	3	4	5	
1	7	1	0	0	
2	29	8	0	0	
3	98	45	3	0	
4	7	15	3	0	
5	9	1	7	6	
	150	70	13	6	239

Total T_3's done = 89

T_3's by strategy = 25

Difference 64

Saving 72%

Normal T_3's = 71%

" by strategy= 17%

FT_4I = 4 tot. = 18	FT_4I - 5 tot. = 14	ERRORS ≃ 7%
T_3's = 3 83%	T_3's = 3 7%	False -ves = 0
= 4 17%	= 4 50%	False +ves = 1 7%
5 0%	= 5 43%	
J.N.Data		

D.A.R.'s as above

Total T_3's done = 538

Total T_3's by strategy = 138

Saving 74%

Difference = 400

Normal T_3's = 71%

Normal T_3's by strategy = 17%

FT_4I	T_3				
	u	3	4	5	
1	35	18	3	0	
2	294	82	19	0	
3	94	185	61	11	
4	9	91	25	13	
5	8	7	3	20	
	440	383	111	44	978

FT_4I - 4 total = 129	FT_4I - 5 total = 30	ERRORS ≃ 27%
T_3 = 3 71%	T_3's = 3 23%	False -ves = 11 ≃ 4%
= 4 19%	= 4 10%	False +ves = 7 ≃ 2.3%
= 5 10%	= 5 67%	
K.E.B.Data		

Performance of original strategy with modified T3 range Figure 4.10

Operation of Current Strategy (Modified Decision-Aiding Ranges)

From J.N. Data — All cases included

TSH Results					FT_4I	T_3 Results				
	1	2	3	u*		u	1	2	3	
25	16	1	2	6	1	21	4	0	0	25
93	18	12	29	34	2	67	24	2	0	93
343	4	18	68	253	3	223	98	18	4	343
107	0	3	27	77	4	59	34	8	6	107
97	0	0	7	90	5	52	11	3	31	97
665	38	34	133	460		422	171	31	42	665

* u - No T_3 or TSH test result for these cases
Periphery of table gives check totals

Strategy Performance for T_3		Savings	Errors: False +ve	Errors: False -ves
Total T_3's Performed	= 243			
Total T_3's by Strat. (1)	= 107	56%	11 (24%)	4 (3.3%)
Total T_3's by Strat. (2)	= 204	16%	0	4 (3.3%)

Strategy Performance for TSH		Savings	Errors: False +ve	Errors: False -ves
Total TSH's Performed	= 205			
Total TSH's by strat. (1)	= 93	54.6%	2 (10%)	4 (4.4%)
Total TSH's by strat. (2)	= 118	42.4%	0	4 (4.4%)

Performance of strategy 1 and 2 on J.N.Data Figure 4.11

Linear Discrimination of T_3 Assay result by FT_4I and Clinical Data

No correction for the interaction between the FT_4I result and the likelihood of a T_3 assay being requested has been made (see text)

Significant variables (J.N. Data)

All patients with a T_3 result (243 cases)*

Variable	Δ in Rao's V	Significance
FT_4I	183	0.000
Lid lag	36	0.000
Diffuse goitre	34	0.000
Multinodular g.	32	0.000
Current T_4	38	0.000
Def^n. Hyper.	14	0.001
Prob. Euthy.	13	0.002
'Other' eye signs	13	0.011
Previous R.H.I.	7	0.038
Carbimazole	11	0.005

Effect of removing discriminant functions on the residual discriminant power.

Removing D.f^n.	Significance
0	0.00
1	0.05

Overall ability to classify data = 89%

		Predicted Class		
		1	2	3
Actual Class	1	186	7	1
	2	13	15	2
	3	2	2	15

Cases may be included, despite missing data, by recoding missing variables to the mean or modal values

Linear discrimination of T3 results by FT_4I and clinical Data

Figure 4.12

No correction has been made for the interaction between the FT_4I results and the likelihood of a T_3 assay being requested.

As before missing clinical data was included by recoding missing values to the mean or modal values. Results from two runs are given, in which cases with missing ages were recoded and then excluded.

Significantly discriminative variables from J.N. Data.

(Rao's V is a measure of variance see S.P.S.S.Handbook)

Variable	Recoding ages		Exclude missing ages	
	Δ in Rao's V	Significance	Δ in Rao's V	Significance
FT_4I	61.5	0.000	24.7	0.000
Current T_4	35.2	0.000	37.6	0.000
Age	25.8	0.000	22.3	0.000
Pituitary Disorder	23.7	0.000	20.9	0.000
Definit. Hypo.	13.1	0.001	9.4	0.009
Prob. Hyper.	7.3	0.025	5.2	0.073
Prob. Hypo.	7.0	0.031	0.4	0.802
Post thyroid surg.	5.7	0.056	7.4	0.024
Males	0.9	0.643	7.5	0.024
Lid lag	3.0	0.226	7.9	0.019

Effect of removing discriminant functions on the residual discriminant power.

Removing D.f^n.	Significance	Removing D.f^n.	Significance
0	0.000	0	0.000
1	0.858	1	0.397

Overall classification rate = 76% 85%

Actual Class	Predicted Class 1	2	3
1	122	7	4
2	22	6	6
3	6	4	28

Actual Class	Predicted Class 1	2	3
1	61	2	3
2	5	10	2
3	1	3	18

Total no. of cases = 205 105

Linear discrimination of TSH results by FT_4I and clinical data

Figure 4.13

J.N. Data Assay Results by Original Decision Ranges

Patients not on therapy

TSH ranges				FT_4I ranges	T_3 ranges				
1	2	3	u		u	3	4	5	
8	0	2	1	1	10	1	0	0	11
5	5	22	5	2	26	8	0	0	37
0	1	21	99	3	89	30	2	0	121
0	1	7	40	4	14	20	4	0	48
0	0	2	23	5	11	1	7	6	25
13	7	54	168		150	70	13	6	242

(u - unknown, no T_3 or TSH assay for this T_4 result)

Selection of Secondary Tests (T_3, TSH) by Clinical Data

Performance of two strategies on all patients in J.N. Data

Clinical Data	Strategy	No. of T_3's	Saving	Errors +ve	Errors -ve
Not Used	1	107	56%	11(5%)	4(2%)
	2	204	16%	0	4
Used	1	83	66%	1 (.5%)	2(1%)
	2	153	37%	0	2

Total No. of T_3's = 243

Clinical Data	Strategy	No. of TSH's	Saving	Errors +ve	Errors -ve
Not Used	1	93	55%	2(1%)	4(2%)
	2	118	42%	0	4
Used *	1	51	75%	4(2%)	6(3%)
	2	95	54%	0	6

Total No. of TSH tests = 205

*Prediction of TSH results can be improved (76 → 85%) if only patients with known ages are used.

Performance of strategies 1 & 2 on J.N.Data Figure 4.14

Action	Assays			Cost
	T_4	T_3	TSH	
1	0	0	0	0
2	1	0	0	1
3	1	1	0	2
4	1	0	1	2.5
5	0	1	0	1
6	0	0	1	1.5
7	0	1	1	2.5
8	1	1	1	3.5

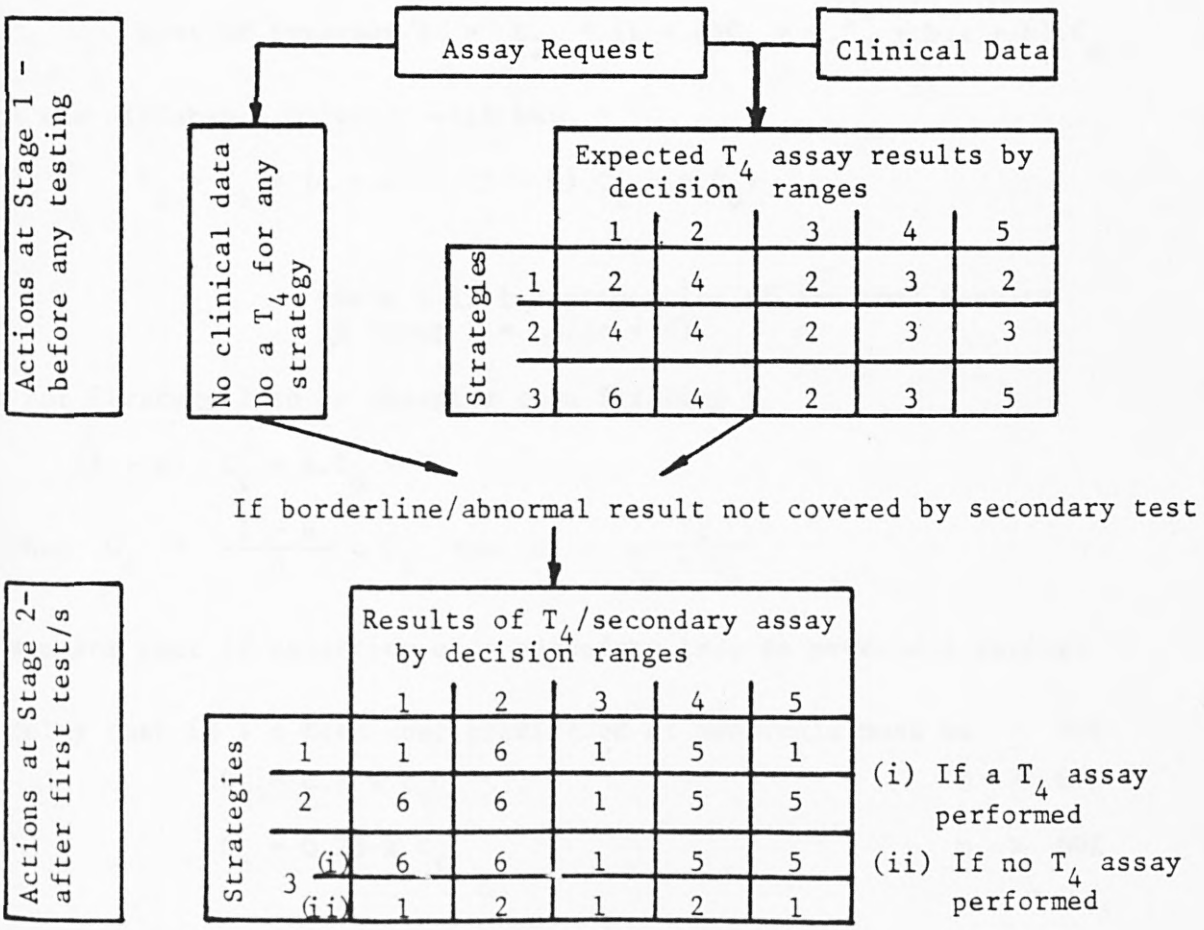
Relative costs assumed:

$T_4 = 1$

$T_3 = 1$

TSH = 1.5

Delay = 1



Actions and costs assumed by the strategies considered

Figure 4.15

Derivation of Loss Function and Effects on a Single Assay

Assuming a simple normal/abnormal result for a screening test (say T_4) and costs C_t for the assay and C_d for the delay in supplying a secondary test after an abnormal screening test result. Two groups are distinguished. G_1 is expected to have a normal result. G_2 is expected to have an abnormal result.

Screening test result:	Normal	Abnormal	
G_1	a	b	Table gives nos. of patients
G_2	c	d	

Two strategies are proposed. Strategy 1 will initiate a secondary test only after an abnormal screening test, while Strategy 2 will give all patients in group 2 the secondary test at once.

$$\text{Cost of Strategy 1} = C_1 = (b + d)C_t + (b + d)\, C_d$$

$$\text{Cost of Strategy 2} = C_2 = (b + d)C_t + c.C_d + b(a + b).C_d$$

Then the difference in costs will be:

$$C_2 - C_1 = (c + d) \quad (1 - n).C_t - n.C_d)$$

where n is the proportion of abnormal results in Group 1 = $d/(c + d)$

Now for Strategy 2 to be cheapter than Strategy 1

$$(1 - n).\ C_t - n.C_d < 0$$

$$\text{Thus } C_d > \frac{1 - n}{n} . C_t \text{ and } n > \frac{C_t}{C_d + C_t}$$

This means that if selection of a secondary test to produce a saving:

If delay cost is 1 x test cost prediction of abnormals must be > 50%

$C_d = 0.5 \times C_t$ n > 67%

$C_d = 0.25 \times C_t$ n > 80%

Derivation of loss function and effect upon a single test decision

Figure 4.16

Linear Discrimination of FT_4I Assay Results by Clinical Data

The discriminator seeks to maximise the distance between classes in the discriminant space. As variables are added in sequence some of the discrim power of later variables may have already been included.

Significant Variables (J.N. Data)

All patients (665)			Patients with Age and Sex Data		
Variable	Δ Rao's V	Sign.	Variable	Δ Rao's V	Sign.
Def^n. Hypo.	41.5	0.000	Def^n. Hyper	46.1	0.000
Prob. Hypo.	32.8	0.000	Def^n. Hypo.	41.9	0.000
Poss. Hypo.	50.8	0.000	Prob. Hypo.	44.3	0.000
Past R.A.I.	10.0	0.040	Poss. Hypo.	23.2	0.000
Current T_4	23.3	0.000	Diffuse G.	20.7	0.000
Def^n. Hyper.	49.5	0.000	Current T_4	19.4	0.000
Prob. Hyper.	41.5	0.000	Lid Lag	17.3	0.001
Lid Lag	11.9	0.018	Carbimazole	16.3	0.002
Carbimazole	16.2	0.003	Prob. Hyper.	11.3	0.003
Past Carb.	12.1	0.017	T.A. Present	5.3	0.023
Diffuse Goitre	6.9	0.144	T.A. Absent	4.6	0.261

Effect of removing discriminant functions on residual discriminant power:

Removing Df^n.	Significance	Significance
0	0.000	0.000
1	0.000	0.000
2	0.166	0.344
3	0.823	0.927

Ability to classify data used to generated discriminator

Overall rate = 54% 60%

Predicted classes

Actual Class	1	2	3	4	5	1	2	3	4	5
1	10	0	15	0	1	5	0	6	0	0
2	9	0	81	1	2	7	3	40	1	2
3	6	0	315	13	9	3	3	189	11	4
4	3	0	87	9	7	1	1	39	12	3
5	1	0	69	2	25	0	3	29	1	18

Linear discrimination of FT_4I results by clinical data Figure 4.17

Loss Function for Prediction of Assay Results
Before Testing for Three Strategies

Costs for Strategy (1) / Strategy (2) / Strategy (3)		Predicted Assay Result by decision ranges				
		1	2	3	4	5
Actual Assay Result by decision ranges	1	1	2.5	1	2	1
		2.5	2.5	3.5	4.5	4.5
		1.5	3.5	1.5	4.5	5.5
	2	3.5	2.5	3.5	4.5	3.5
		2.5	2.5	3.5	4.5	4.5
		3.5	2.5	3.5	4.5	5.5
	3	1	2.5	1	2	1
		2.5	2.5	1	2	2
		1.5	2.5	1	2	1
	4	3	4.5	3	2	3
		4.5	4.5	3	2	2
		5.5	4.5	3	2	3
	5	1	2.5	1	2	1
		4.5	4.5	3	2	2
		5.5	4.5	1	2	1

Decision Ranges

1. Hypothyroid
2. Borderline low
3. Euthyroid
4. Borderline high
5. Hyperthyroid

Relative Costs

T_4 assay = 1
T_3 assay = 1
TSH assay = 1.5
Delay = 1

Loss function used to establish costs of strategies

Figure 4.18

A Comparison of Three Assay Selection Strategies

for initial assay selection with and without clinical data(C.D.)

Patients taken from J.N. Database

Use of Clinical Data		Strategies	Number of FT_4I Results divided into their decision ranges					Total Costs	Total Number of T_3 or TSH Tests	
			1	2	3	4	5			
			11	53	210	56	51			
			Cost of Results By Decision Ranges							
No C.D.		1	11	185.5	210	168	51	625.5	109	
		2	38.5	185.5	210	168	153	755	171	
		3	16.5	185.5	210	168	51	631	171	*
C.D. Used		1	11	185.5	227.5	157.5	56.5	634	129	
		2	33.5	178.5	234	156	138.5	740	198	
		3	16.5	187.5	227	160	62.5	653.5	198	*

Costs Assumed:

Delay Cost = 1

T_4, T_3 Assay = 1

TSH Assay = 1.5

Costs taken from success of linear discrimination of FT_4I results by clinical data

* This strategy omits the T_4 test for clearly abnormal patients.

Effect of clinical data on strategy performance Figure 4.19

THE MIDDLESEX HOSPITAL DEPARTMENT OF NUCLEAR MEDICINE

N.M. THYROID FUNCTION ASSAYS

All / Most features unchanged since last request on this type of form

Record PRESENT STATE. Mark ONE of each category

Clinical
- ☐ Definitely \
- ☐ Probably −HYPO
- ☐ Possibly /
- ☐ Probably −EUTHY
- ☐ Possibly \
- ☐ Probably −HYPER
- ☐ Definitely /

Goitre
- ☐ Thyroid normal
- ☐ Diffuse enlargement
- ☐ Multinodular enlargement
- ☐ Single nodule palpable
- ☐ Proven neoplasia
- ☐ Thyroid not palpable

Previous Therapy
- ☐ None
- ☐ R / A I therapy
- ☐ Surgery to thyroid
- ☐ Surgery to pituitary

Thyroid Eye Signs
- ☐ Not present
- ☐ Present

Pituitary / Hypothal Disorder
- ☐ None
- ☐ Possible / Probable
- ☐ Definite

Present DRUG THERAPY: Mark ONE or MORE

DOSE
- ☐ None
- ☐ T4 .....
- ☐ T3 .....
- ☐ PTU / CBZ .....
- ☐ Glucocorticoids.....
- Type .....

- ☐ Pregnancy or oestrogens
- ☐ Lithium
- ☐ Iodide compounds
- ☐ Other antithyroid drugs

Form No. M 54

No. .....

Surname

First Names

Date of Birth

Mr.
Mrs.
Miss

Ward / Dept.

Consultant

Return to

Date

Any additional Clinical Comments

Assay Required:
- ☐ T4 ..... nmol / L
- ☐ T3 ..... nmol / L
- ☐ TSH ..... mU / L
- ☐ Free T4 ..... pmol / L
- ☐ Free T3 ..... pmol / L

JB-B6865

Revised version of thyroid request form currently in use Figure 4.20

CHAPTER 5

Relations within Clinical Data drawn from a Routine Laboratory Record

5.1 Introduction

Chapter 4 described the methodology and immediate impact upon assay selection of the routine collection of clinical and biochemical data. This chapter examines the characteristics and relationships within that data base in greater detail. It was suggested that one of the benefits of such a data base was that further analysis of the sample might show distinct, and perhaps unexpected groupings or relationships among patients. These might in turn have implications for the interpretation of assay results or therapy decisions or as stimulus to further work. Patient samples from differing groups (ie. elderly patients, inpatients) or from differing types of physician (general practioners, surgeons) may reflect not only their own condition but require differing emphasis depending upon the request service. The two samples available here can be expected to show a greater frequency of abnormal results than a normal population but the comparison should suggest useful indicators and the effects of therapy. A substantial population survey had recently been reported in Tunbridge et al (1977) and Evered et al (1978) which is used in this text under the joint reference of Evered et al (1978). A further concern was whether routine examination of assay results would suffice to check that the decision ranges, originally established by Britton et al (1975), were still appropriate to the new pilot study data base. As the data from Britton et al (1975) constitute a hospital-wide sample, it could be used to extend some results and consider factors wich could not be included in the pilot study sample drawn from the patients attending a particular consultant (J.N.)

The biochemical and clinical variables were first examined independently before the possible interdependences were considered. The structure of the expected dependentces is largely outlined in figure 5.1. Where possible, results from the Evered survey and the earlier Britton study were also included and commented upon.

5.2 Analysis of the Biochemical Measures

In this section results for determinations of T4, T3 and TSH levels requested in the two patient samples are examined in the light of known measurement error, the effects of patient selection and the interaction between assays actually performed and the decision ranges used.

5.2.1 The T4 Assay, Distribution of Results

Evered et al (1978), in an extensive survey, have shown that T4 and T3 results in their general population do not significantly deviate from a Gaussian distribution. The T4 results show a relative standard deviation of 25%. If an additive model of errors is used, then the underlying individual patient variation is of the order of 15% combined with an assay error of 20%, assuming that the T4 results do follow a Gaussian distribution. The distributions of the FT4I data are shown along with the T3 and TSH assay results in figures 5.2 (data from the J.N. study) and 5.3 (data from the K.E.B. study). The T4 assay is generally used as a screeniing test, thus characterising the whole sample. Simultaneously an estimate of protein binding capacity is provided by a T3 Resin Uptake test to produce an index of the free hormone levels (FT4I). As this 'corrected' T4 value is available, it is normally used in preference to the basic T4 measure. Some idea of the effects of this correction can be obtained from figures 5.4 and 5.5 of plots T4 versus FT4I. The slight curvature of the plot can be ascribed to the non-linear nature of the T3 Resin-Uptake test. Otherwise the results remain close to the + - 10% lines drawn. Pregnancy or raised oestrogen level, age and genetic predisposition are all known to alter plasma protein levels and hence distort the T4 result. The first two groups can be identified in this study, but as the results in figures 5.4 and 5.5 show, significant differences between the FT4I and T4 results cannot be established . It seems that there is little benefit in the calculation of an FT4I except for special cases where an unexpected T4 result or the presence of altered serum binding proteins due to steroids or renal failure, etc., indicates such a need. The Evered (1978) survey confirmed that overt symptoms of thyroid disease were reflected in alterations of the thyroid hormone levels. In these hospital samples (the K.E.B. and J.N. studies) a much broader and probably positively skewed distribution was expected since, among the

many unwell and treated patients, the hyperthyroids both occurred more frequently (in consequence of the higher incidence of this disease and the need to follow-up such patients) and would also have the greater change in plasma iodothyronine concentrations. In addition the physicians could be expected to avoid testing euthyroid patients, thus leading to a rather flattened distribution. The skewed effect appeared but so did a pronounced 'peaking' in the T4 distribution (figures 5.2 and 5.3). When the T4 results are broken down by therapy (figure 35) a sharp, near normal distribution for patients not on therapy can be seen superimposed upon the much broader characteristics of those on therapy. Figure 5.6 shows the effects of removing these patients for whom there was an indication that they had been clinically assessed as being other than euthyroid. A logarithmic transformation of the T4 or T3 results failed to produce a closer fit to a Gaussian distribution.

The reduction towards a normal distribution achieved by selection of the patients implies that a basically normal distributed variable is being distorted by clinical suspicion and therapy. The near Gaussian group indicates, however, that physicians are often merely excluding the possibility of thyroid disease. The much greater variance in results from treated patients not be entirely due to early changes occurring during therapy, but may reflect an underlying failure to achieve biochemical normality. Observation of these patients over time would give a clearer indication of the success of the therapies applied. The effects of differences in the sample T4 means for the decision-aiding-ranges (d.a.r.s) which were derived from the data from the K.E.B. study are discussed later.

5.2.1. Secondary Test Result Distributions (T3 and TSH)

Apart from the large proportion of patients on therapy who are included, the T3 and TSH distributions of figure 5.2 are further distorted by changes in assay variance over the range of analysed dose and the selection of these tests according to the suspicion of the particular physician and the current test strategy. The appearance of a T3 or TSH result is particularly dependent upon the previous FT4I result. Figure 5.7 tabulates the frequencies of T3 and TSH assays against their associated FT4I results broken down into the original decision-aiding-ranges. There is an obvious increase in the T3 request

rate for FT4I results in the borderline high range (4) and for TSH results in the lower FT4I ranges (1 and 2). To correct for this dependence upon the FT4I result, the T3 and TSH results were weighted to give an occurrence rate equal to that obtained after a FT4I results in the euthyroid range (3).

The weighted and unweighted T3 results for patients not undergoing therapy (figure 5.8) were truncated beyond two standard deviations and a new estimate of mean and standard deviation obtained by fitting the cumulative percentages to a Gaussian distribution. Weighted data showed a better fit to the Gaussian curve as would be expected, but the de-emphasis of T3 results after a borderline T4 result had comparatively little effect, implying again that many of these patients were euthyroid. The T3 mean obtained was (1.70nM) against the (0.66 nM) of the Evered survey and 0.93nM of the K.E.B. study. The T3 data of figure 5.8 reveal a negative skew which suggests that truncation had excluded a significant number of T3 results. It seems clear, however, that the J.N. data show a reduction in the mean and the deviation of T3 results which have implications for the decision-aiding-ranges.

The TSH results, both weighted for FT4I results and unweighted, are given in figure 5.8. The approach used in the K.E.B. study of locating the lower limit of the borderline range just above 84% of patients considered euthyroid and not on treatment was followed. (In a Gaussian distribution, 84% of results will be below +1 S.D.). The TSH value obtained (9 mU) was close to that used in the K.E.B. study (11 mU) and no changes appear to be indicated.

5.2.3 Assay Interactions

Strong correlations are expected between these assay results. A large proportion of circulating T3 arises from conversion from T4, so a simple model, including conversion proportional to peripheral T4 levels and with fixed relative rates in the glandular production of these hormones, would produce a simple linear regression which passed through the origin. Current evidence suggests that T3 levels are well maintained despite severe changes in T4 concentrations, either because the TSH stimulated gland produces relatively more T3 when levels fall, or by reduced peripheral conversion when large amounts of T4 appear.

These two factors probably explain why the regression line of figure 5.9 fails to pass through the origin. The underlying T3/T4 relation arising from peripheral conversion should be seen in patients on T4 therapy once TSH levels return to normal. Figure 5.10 shows that these patients consistently show a low T3/T4 ratio which can also be observed in T4-treated patients in the K.E.B. study (figure 5.11). Both figures include for comparison a simple linear relation, passing through the origin, which predicts quite well the T3/T4 ratio for patients not on T4 therapy. As figure 5.12 shows, the T3/T4 ratio appears to fall as the FT4I result increases for all patients, but the ratio is lower over the whole range (figure 5.13) for patients on T4 therapy. Reduction of T3 glandular output cannot be expected to account for these changes if current estimates of T3 production are correct. The figures show the effect upon the T3/T4 ratio of the cessation of glandular T3 production. The implication is that the circulating T3 concentration is a factor in peripheral conversion.

Figures 5.14 and 5.15 show the relationship between serum TSH concentration and T3 and T4 concentrations. An exponential trajectory is shown in each case but considerable variation is apparent. Part of this variation arises from transient responses of patients recently given T4 who still have high TSH concentrations, part from those with low TSH who still have high TSH concentrations and part from those with low TSH and thyroid hormone concentrations who have pituitary disorders.

5.2.4 Effects upon the Decision-aiding Ranges

The FT4I results described in section 3.2 point to an increase in mean value of FT4I and, therefore, to changes in the break points of the relevant decision-aiding ranges. Similarly the rather smaller spread of T3 results implies a need to narrow the T3 d.a.r.'s in figure 5.9 seems to confirm this from the large number of 'normal' T3 results in FT4I range 4 and the rarity of any clearly abnormal T3 result. Whilst this might bring the ranges into sensible correspondence with the projected T3/T4 relations (figure 5.16), it retains the unrealistic division of the T3/T4 space into blocks. In figure 5.16 the results described later in sections 5.3.2 and 5.3.3 are used to update the previous estimates of the borderline regions. The ellipses indicate one and two deviations from the mean T4 and T3 values. Patients on T4 therapy who lie outside

these regions must of course be eliminated from this d.a.r. classification at least on the basis of T4 concentration measurements: T3 results can be of value in assessing the thyroid status of such patients, however.

5.3 Clinical Data

Figure 5.17 shows the clinical variables conveniently broken down into 3 groups. Group I consists of the minimum of information which can reasonably be expected to be made available for a normal, general request and consists of the clinical assessment made by the physician and the therapy category for the particular patient. Usually the age and sex of the patient and the source of the request (i.e. ward/out-patient, G.P./Endocrinologist) would also be routinely available: these variables form Group II. In the J.N. study, only one consultant was involved so the 'Request Source' was limited to the Ward or Clinic. Finally the four additional clinical signs which were recorded in the J.N. study are consigned to Group III.

5.3.1 The Incidence of Clinical Data

Figure 5.18 shows the incidence of each clinical variable in the J.N. study a 'U' indicating a missing observation on the patient. Missing observations normally constituted approximately 10% of the total, the exceptions being age (= 40%) and Goitre Status (= 20%). Physicians were reluctant to add either the age or sex, but the sex could usually be deduced from the patient's name. No obvious bias in the occurrence of missing ages (for example, between the sexes) was observed so it was assumed to be random. The absence of goitre records was traced to the lack of a 'non-palpable' category on the request form and so the physician made no response in such cases. Apart from these exceptions, a responsse rate of between 85% and 95% was maintained for each variable for this group of patients.

'Error rates' - once obvious coding/punching mistakes were rectified - were dificult to estimate. Confusion did seem possible with the clinical assessment. This was taken to be the overall assessment by the physician of current thyroid status based upon the presenting signs and history of the patient. Results appeared, however, with 'Definitely

hyper/hypo' assessments and yet normal hormone levels. This probably arises from the lag before clinical changes follow the biochemical state. It is possible, however, that some clinicians recorded the patient diagnosis rather than their assesment of the patients current clinical state as a number of cases had no therapy recorded.It is likely then that these cases were erroneously coded for clinical assessment or therapy, either by mistake or missunderstanding. Other explanations are possible but a detailed examination of patient records would be needed to confirm the true error rate on these forms. The rates of successful completion of the forms for the clinical variables in the K.E.B. study are given in figure 5.19.

5.3.2 Univariate Charcteristics

Clinical assessment can be considered to be an ordinal variable. The majority of requests for thyroid hormone assays were for patients assessed as being 'probably euthyroid' (57% in the J.N. study) with the 'probably/definitely' abnormal requests representing together less than 10%. A large proportion of these apparently normal cases are on long-term follow-up and are on, or have been on, treatment. A third of all cases were on T4 therapy (332) and 20% on Carbimazole (200). The predominance of T4 therapy, despite the higher expected incidence of hyperthyroidism (Evered et al, 1978) occurs because of the long term nature of T4 replacement therapy and the occurrence of post treatment hypothyroidism in some hyperthyroid patients. This tends to arise after ablative antithyroid therapy and (it is suspected) after severe hyperthyroidism. Patients with a non-toxic goitre will also generally be given T4 therapy. About 20% of cases have had previous ablative therapy either by radioactive iodine (R.A.I.) or surgery. These patients will have had antithyroid drugs before ablation and failed to remit. Patients who are recorded as previously having had antithyroid drugs are normally off drugs and are being checked for relapse.

From Group II, data which include the age and sex distributions of the two samples (the K.E.B. and J.N. Studies) can be compared. The data from the K.E.B. study are noticeably different: these data include a substantial geriatric population. Evered et al (1978) found a ten-fold ratio between obviously abnormal females compared with males while the ratio between the sexes in the J.N. study is only about three

fold. This, however, probably reflects the sampling of a general population compared with the hospital sample of the J.N. Study. The 'request source' for the data in the J.N. study was found to be unsatisfactory since many reports were returned directly to the physician rather than to the ward. The identification of physicians in the K.E.B. study, however, allowed six groups to be discriminated (endocrinologists, radiologists, surgeons, geriatricians, hospital physicians and G.P.s) apart from picking out cases arising specifically from the same physician (J.N.) as in the second study.

Group III consisted of two specific signs (Goitre and Eye), and assessment of pituitary disorder and the report of an antibody test. This test was not done or the result was not available for nearly 50% of requests, the rate of testing being dependent upon other signs. The other three signs were normal in about 60% of cases. If the unknown (including non-palpable) and normal goitre categories are combined the incidence rate is close to the 8% observed by Evered et al (1978) - suggesting that goitre is a secondary cause of the patient presenting and that it is removed by treatment. Selection of antibody tests makes the true occurrence of antibodies uncertain however, it was positive for thyroid antibodies in about 60% of the tested group and 27% of the total sample. As the Evered survey found a rate of under 25%, it seems likely that antibodies are a more consistent accompaniment of specific thyroid disease symptoms and treatment.

5.3.3 Relations Between the Clinical Variables

The low rates of abnormal signs severely limit the degree to which interactions can be confirmed. Three specific sets of relations are of interest and have been examined.

(i) Inter-relations between the clinical signs.
(ii) Age and sex dependence of the sample signs.
(iii) The prediction of the clinical assessment from these clinical signs.

The clinical variables were redefined producing 36, mainly binary, variables from the original eleven. The T4, age and sex distributions of missing values for each variable were checked and were usually found

to be close to those of the mean value for that variable. Missing values were included by recoding either to the mean or mode value as appropriate, or used to exclude that case from further processing.

Examination of the simple correlations between variables pointed to distinct groupings which could be isolated with the aid of factor analysis. Usually, however, these relations and others of clinical interest were examined in more detail. The full matrix of correlations is included in the appendix but a reduced version is shown in figure 5.20(i) and shows that most interactions were of a low order and that interactions between signs were of similar magnitude to those relations with the clinical assessment and the T4 result.

5.3.4. Interactions Between the Four Additional Clinical Signs

Figure 5.20(ii) shows the clinical signs as a recorded subset of the clinical variables, emphasising the grouping of correlated signs. These correlations are significant for the number of cases considered if the selection of antibody results is ignored. As can be seen, diffuse goitre and exophthalmos are linked via the presence, and presumably the testing, of antibodies associated with lid-lag, which is in turn linked via goitre. The few cases of nodular goitre tend to be associated with negative antibody tests. The significance of these associations can be assessed from figure 5.21 where antibody occurrence, eye signs and goitre status have been cross-tabulated.

The selection of antibody tests is clear. In the absence of abnormal goitre signs 41% of cases have an antibody test result, whilst 61-67% of cases have been tested when abnormal eye or goitre signs are present. The Evered survey found that the presence of goitre signs raised the frequency of a positive antibody result from 45% without signs to 65% with positive goitre signs. A similar, though smaller, change was seen in these data (from 48% to 56%). Eye signs (not reported for the Evered survey) were more frequently seen with a positive antibody result (22% for negative antibodies; 27% of positive antibodies). The presence of diffuse goitre raised the rate of eye signs from 14% to 40% in the females from 17% to 60% in the males.

As would be expected, the possibility of pituitary dysfunction

(usually under-activity) was not associated with these signs which are mainly indicators of hyper-thyroidism.

5.3.5 Age and Sex Dependencies

The high (40%) rate of missing data on ages, limits the value of these data, but assuming a random effect of these missing values, figure 5.22 gives the occurrence of each sign broken down by age and sex. The age divisions used (at 40 and 60 years) reflect the distribution and sparsity of data. The rates of occurrence of abnormal signs with age, both overall and on the basis of sex, were checked against the whole sample except for the variable indicating antibodies, where a larger proportion of the positive results were found not to have an age supplied.

Diffuse goitre was most common in young females, 28% declining to 12% after 60 years (the Evered survey showed 29% declining to 12%). Nodular goitre was rarer rising from 5% to 9% in the later decades which was similar to the Evered survey (5% to 4%-7%) apart from a fall seen in the survey for those over 75 years (5%). In males, the numbers were much lower, but had a similar pattern to the survey data. Broadly, therefore, the similarity in goitre rates between this hospital sample and the Evered survey is maintained for age and sex divisons.

In the J.N. study, the raw appearance rates of positive antibody results show an age dependent increase for both sexes. If, instead, the percentage of positive results is calculated on the basis of those tested, this increase is greatly reduced, suggesting some success in the clinical assessment of symptoms.

Eye signs were not recorded for the Evered survey. The J.N. survey showed that female exophthalmos declined from 20% to 7% with age, while the other signs and all occurrences in males were at very low rates. Pituitary disorder falls overall with age but when broken down by sex shows a generally high rate in males which increases with age.

The occurrence of previous and present therapies is age dependent, as would be expected. Abalative surgery and T4 therapy tend to predominate in older patients, whereas previous treatment with

antithyroid drugs and current carbimazole therapy are more common in the younger patients.

5.3.6. Association of Clinical Signs with the Clinical Assessment

The simple correlations of figure 5.20(i) and the diagrams of figure 5.23 give an indication of the importance of these clinical signs in the clinical assessment. For each clinical assessment (CO-6, where C3 = euthyroid), the difference between the presence and absence of a particular sign (Si - So) at each C-value is plotted. In this way the effect upon the clinical assessment of changes in the clinical signs is not obscured by the consisently large proportion of 'probably euthyroid' assessments. Without time-series data, many of the implications of changes in therapy, for example, will be lost, but some effects do remain. Patients on T4 therapy, are more often classed as euthyroid, presumably reflecting the long-term nature, success and stability of this therapy. A history of antithyroid drugs is likely to raise the suspicion of a relapse, while ablative treatments carry the risk of subsequent hypothyroidism. It may be that the physician, while recording these signs, acts as a filter selecting out instances where a sign is confounded by other factors. The lack of clinical signs for hypothyroidism means that the clinical assessment is the only indicator in these data available for these cases thus increasing the relative value of the clinical assessment made by the physician.

Regression analysis can be used to estimate the proportion of the variance in the clinical assessment 'explained' by the clinical signs. A linear regression on these data suggests that nearly 20% of this variation is related to the clinical signs. The other 80% arises from other factors not considered, or higher order effects, possibily time dependent relations within the clinical signs. The relative contributions of each sign can be seen from the results of the regression analysis in figure 5.24. A linear discriminant analysis, in which the clinical signs are used in an attempt to classify the clinical assessment and the clinical signs, demonstrates that the discriminatory signs can be grouped into those indicating abnormality and those specifying hyper- and hypo-thyroidism. Figure 5.25 shows the centroids of groups of patients classified by the clinical assessment in the space produced by the first two discriminant functions. The distance between

centroids is an indication of differentiation between classes and the proximity of the hypothyroid assesments suggests a lack of indicators of hypothyroidism among the clinical signs. Further details of the discriminant technique used are given in the S.P.S.S. Handbook. It is important to note that identification and testing of the discriminant functions took place on the entire set of data. This 'testing on the training set' will give rise to a favourable bais in the apparent performance of the classifier. A more realistic evaluation would employ the 'leave one out' technique by identifying the discriminator on all data except the case to be classified. The results presented here should therefore be viewed as descriptive of the sample data and as establishing an upper limit on the performance of a simple linear discriminative model.

In the following section, the ability of the clinical assessment and signs to predict the likely outcome of an FT4I assay will be considered.

5.4. Relations Between Clinical Variables and Biochemical Measures

This section details the relations between the clinical variables and the biochemical measures, emphasising the ability of the clinical variables to predict the T4 or FT4I result. Describing the interactions of the clinical variables with the T3 and TSH results is more complex, because their selection is dependent on the physician's request, his stated suspicions and the outcome of the T4 test.

5.4.1 First Order Relationships

Figure 5.26 illustrates the model used to describe variation in the T4/FT4I results. Though the precision of the assay is somewhat variable, the results given in section 5.3 suggested that between 20% and 30% was a reasonable estimate of the overall figure for the FT4I error rate. This can, therefore, be expected to contribute contribute 10% to 25% of the total FT4I variance which is observed. The residual variance then arises from changes in the 'true' T4 level, the biochemical state of the patient which can to some extent be predicted by the clinical variables. The residual uncertainty is then an indication of the information supplied by the T4 test. Whether the

reduction in uncertainty produced by the clinical variables can be useful was examined in chapter 4.

As the clinical variables are inter-dependent, a simple linear regression is likely to produce confusing results. Unfortunately, the signs are too sparse to determine the significance of many of these dependences directly. Partial correlations have been used to check the stability of these relations and the regression used. In particular, it would be expected that many of the implications of the clinical signs would be included in the overall clinical assessment. Chapter 4 confirmed that the signs could be indicators of abnormality generally and hyperthyroidism in particular, about 10% - 15% of the assessment. Figure 5.27, therefore, shows the correlation with FT3I results when 'controlled' by the clinical assessment. This checks the remaining information after the clinical assessment has been removed. Only the diffuse goitre sign remains significant at a 10% level. As the regression analysis progressively includes additional variables, some of the explanatory power of the later variables will already have been incorporated by the earlier variables. Instead of a simple regression of clinical assessment upon FT4I the individual assessments are redefined as variables, C0 to C6, to check their individual contributions.

Figure 5.28 shows the results of a linear regression of the six abnormal clinical assessements on FT4I. The assessment can explain about 20% of the FT4I variance, but the category "possibly hyperthyroid" does not make a significant contribution. Presumably both this and the "probably euthyroid" category represent similarly low levels of suspicion, the 'hyper' state being picked for those on carbimozole therapy the 'euthyroid' resulting for those on T4 therapy. This seems to be confirmed by the actual distribution given in figure 5.29. These are also obviously non-Gaussian, however, which alters the certainty of the estimates given. The relation between FT4I and clinical assessment is also indistinguishable from linearity on the basis of analysis of variance. As the mode is only strongly affected by 'extreme' clinical assessments, which are not of common occurrence, for maximum likelihood decision-making these small changes in FT4I with clinical condition give little or no significant benefit. If the requirement of predicting the most likely result is replaced by prediction of groups likely to have an

abnormal result there may still be a useful return even if a result in the normal range remains the most common outcome. This is discussed in section 7 but it does suggest that further work may be useful and, thus, the effects of the other signs have been examined.

Even if regression analysis is extended to the complete set of clinical variables, only 26% of the total FT4I assay variance can be explained. Apart from the clinical assessment, only some of the therapy signs, diffuse goitre and eye signs, make a significant contribution. A summary of this regression analysis and that carried out for the clinical signs alone which accounted for 12% of the FT4I variance is given in figure 5.30. Age data were not significant either for replacement of missing cases by the mean or deletion of these misssing 40% cases entirely.

Figures 5.31 and 5.32 show the effects of the therapy categories on the FT4I distributions. In both the J.N. and K.E.B. data (see figure 5.35) there is a tendency for high-to-normal T4 values to be associated with T4 therapy - whilst the clinical assessment is usually 'euthyroid'. This is not reflected in the T3 results, as would be expected, and figure 5.33 shows the regressions obtained for FT4I on T3 for different therapies. The T4 results are not useful in predicting the clinical status of T4-treated patients, (this is considered further below). The previous therapies tend to shift the assay result as expected upwards for previous carbimazole treatment and downwards for the ablative treatment. These effects seem to be largely absorbed by the clinical assessment but they are the only significant hypothyroid indicators in the data base.

5.4.2 Age and Sex Dependences

The age/sex dependences of the whole range of assays are given in figure 5.34. Comparing the results of the J.N. study with those of the Evered survey (1978), similar rises in T4 and TSH and fall in T3 are observed but with an increased age dependence. These age dependences are much stronger in the data of the K.E.B. study, probably being correlated with the older and more generally unwell sample of patients. Of particular interest is the breakdown of FT4I results by decades given in figure 5.35 which shows a distinct bi-modality in patients aged over

60. To some extent this pattern is seen throughout the age range. This effect is not seen in the data of the J.N. study nor among the J.N. patients within the K.E.B. data-base. Patients showing increased T4 tend to come from the geriatric sample.

If patients from the K.E.B. study on T4 therapy are examined, then a similar though not co-incident peak is seen (figure 5.35), and these data also show the lowered T3/T4 ratio seen earlier in the J.N. data for such patients. It is possible, therefore, that the effects of age and T4 therapy on the T3/T4 ratio are related. The regression lines in figure 5.36 for patients on T4 therapy are superimposed upon a scattergram of patients aged 65 and over. Whilst the proportion of patients known to be on T4 therapy is very low in the K.E.B. data, it is likely that many others are actually receiving T4 therapy.

5.4.3 Other Clinical Signs

The other effects of clinical signs upon FT4I are detailed in figure 5.37, from which it can be seen that only small changes in distribution occur. Sub-samples of patients selected by therapy show similar distributions. Generally, therefore, the presence of an abnormal sign simply increases the possibility of an abnormal result. It is still possible that combinations of signs, perhaps for patients on therapy, will be particularly useful. Figure 5.38 shows the FT4I results predicted by the combination of eye and goitre signs, but in this case there is an increase in variation and reduction in numbers of samples that makes the significance of possible relations uncertain. These combinations of variables were included in regression and partial correlation analysis with results little different from those obtained with the simple variables.

Having examined these relations and determined to some extent their possible clinical significance it remains to use them to predict the results of the T4 assay. Redefining the T4 results in terms of decision-aiding-rages and using discriminant analysis or pattern recoginition is a direct approach to this problem.

5.5. Conclusions

The results of analysing the pilot-study data presented in this chapter have been limited by the sparsity of cases within interesting sub groups and particularly by the lack of time-series data. Both problems can readily be overcome by the accumulation of routine data through the implementation of a patient records system as part of the enhanced service operation described in chapter 3. There are sufficient data, however, to conclude that sub-groups can be identified within the sample whose characteristics have implications for interpretation and therapy. In particular, the normal relationship between the T3 and T4 assays, which seems to hold for untreated patients and those on carbimazole therapy appears disturbed in patients receiving T4 therapy. This effect is most clearly seen in the unexpected bimodality observed in T4 results from older patients in the data of the Britton study. It is possible that some form of peripheral control of deiodination of T4 to T3 is being observed. It would be particularly interesting to be able to examine the effect of differing T4 dosages upon individual T3 and T4 values over an extended period. A special study may finally be necessary, but continuous data aquisition could do much to suggest both the processes involved and the nature of the study to be undertaken. Enhanced assay operation would make such investigations simple since, apart from providing accessible data, specified groups or individuals could automatically be picked out for a full battery of measures or a programme of special consultations.

Evidence of other dependences in thyroid hormone levels, such as age and sex, remains equivocal with other authors (Evered et al 1978) pointing out that changes in hormone levels have been observed in surveys of hospital populations. It has been shown here that the untreated groups seem similar, in distribution, to the general population. It would therefore seem likely that as patient therapy and general health factors are included, appropriate differences in the degree of age and sex dependence will be observed. Though examination of these data has raised many questions the results obtained so far provide stimulation for continued work and data collection.

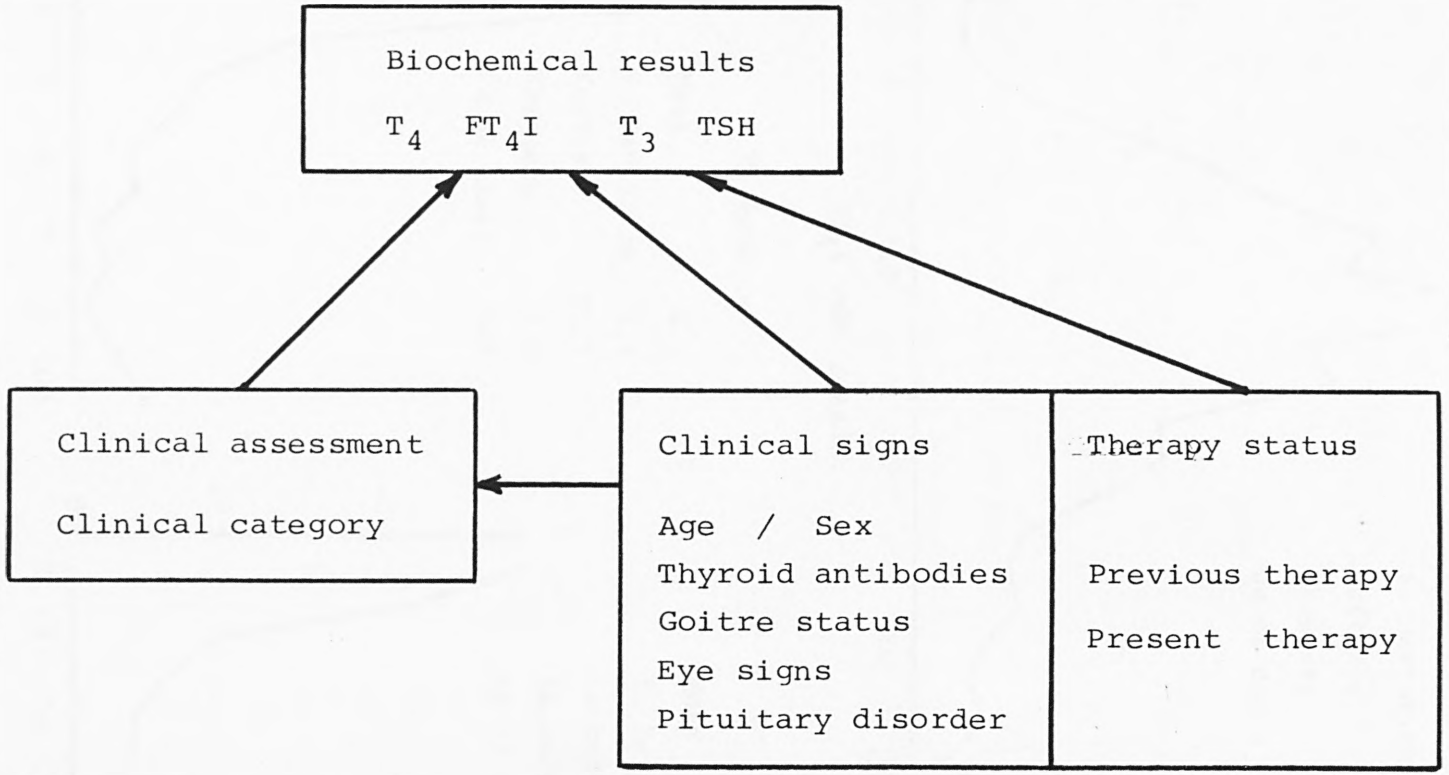
The data of the Britton study also suggest that the request source is likely to be of importance. Identification of the requesting

physician and ward or clinic can not only indicate the probable patient state but may also provide comment upon the value of the clinical judgements made. Interpretation of these factors is likely to require considerable medical knowledge. Patients observed after thyroid surgery, for example, are likely to show very wide fluctuations. Other patients may be tested by a cautious physician merely to eliminate a doubtful diagnosis from further consideration. These effects tend to decouple the clinical statements from the observed biochemistry and require the inclusion of historical data.

Among the clinical signs collected during the pilot study the goitre and eye signs seemed particularly useful, including much of the information associated with measurement of the presence of thyroid antibodies. The correlation of antibody results with goitre and eye has been pointed out earlier as a reason for this. The clinical assessments and the therapy statements seem to be reliable, to contribute to assay selection and be neccessary for the distinction of patient groups. Two additions which should be considered to the clinical data are inclusion of drug dosages and some more general statement of patient "well-being". Drug dosage would be particularly useful and should not be difficult to obtain. The degree of compliance is oftern considered an important source of uncertainty. The input to the patient is, however, the physician's instruction. The option of compliance, giving rise to a scatter in response or a tendency for success to decline with time or increasing dosage, then represents the patient response. Encouragement, stricter regimes, more acceptable medication are possible inputs whose effects may be monitored through routine observation. Finally a separate study might be justified to confirm the impression that lack of compliance was the important factor. Subjective statements from the patient have not been proposed here as they may be affected by many factors independent of thyroid state. The improvement of the perceived clinical state is however the aim of therapy and some indication of the patient's opinion might be interesting and useful feedback. This is a possible site for the application of patient screening programms to ask a series of routine questions at each consultation. One advantage of such a system is the comparative impersonality of the system which may encourage a more 'objective' response from the patient. An alternative is to combine a query programme with a small number of tests or observations carried out by nursing staff. The results and comments can

be passed on to the physician as a preliminary screening and retained as part of the routine clinical database.

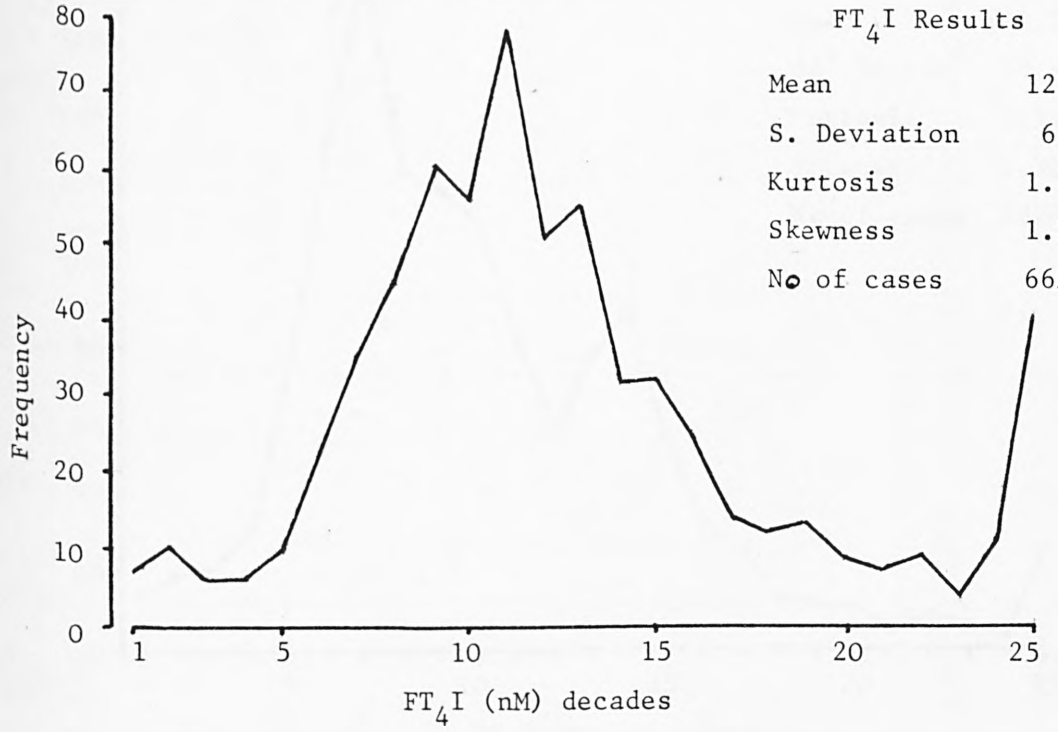
The absence of time series data had been mentioned particularly as such data allow more complex models of behaviour to be examined and hence problems of measurement and control to be introduced. The next two chapters are concerned with development of models of thyroid state and the examination of changes in thyroid hormone levels during therapy. In chapter 6, the current models of thyroid hormone dynamics are examined in an attempt to identify structures suitable for clinical application. Chapter 7 introduces a reduced model for clinical use and attempts to identify its structure from data gathered to study the effects of antithyroid drug therapy on patients suffering from hyperthyroidism.

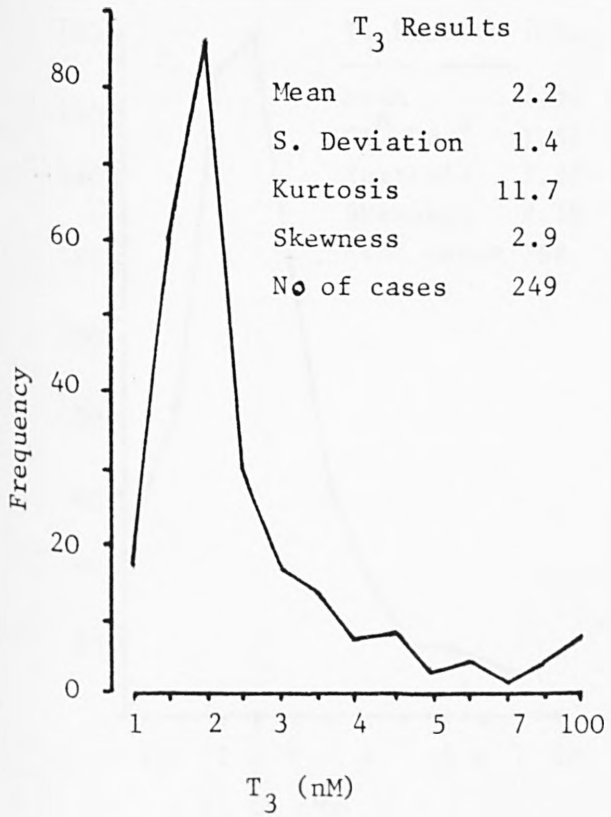


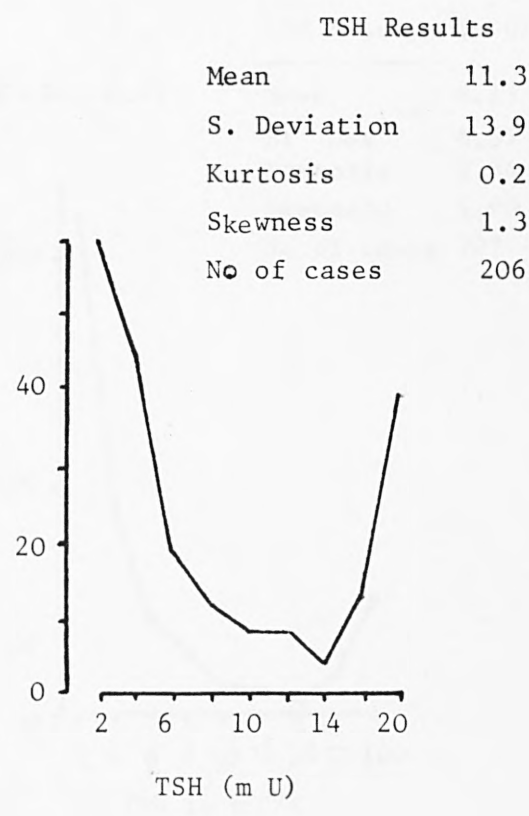
Proposed model of the relations between biochemical and clinical data

Figure 5.1

Frequency Polygons of FT_4I, T_3 and TSH Assay Results in J.N. Data



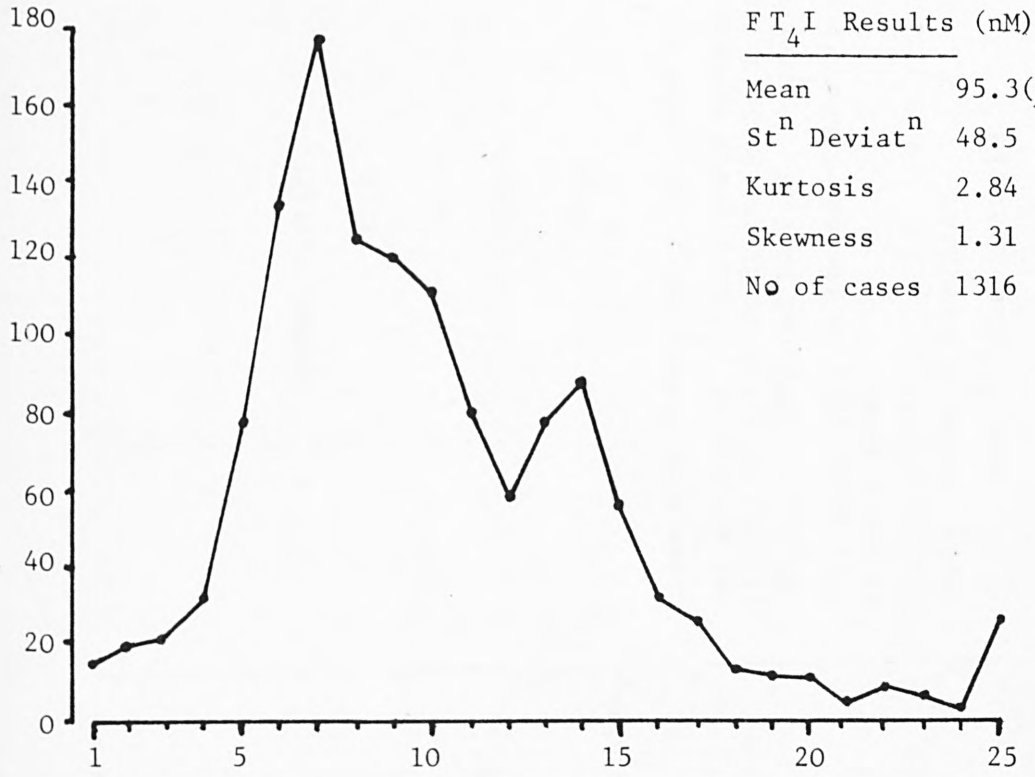




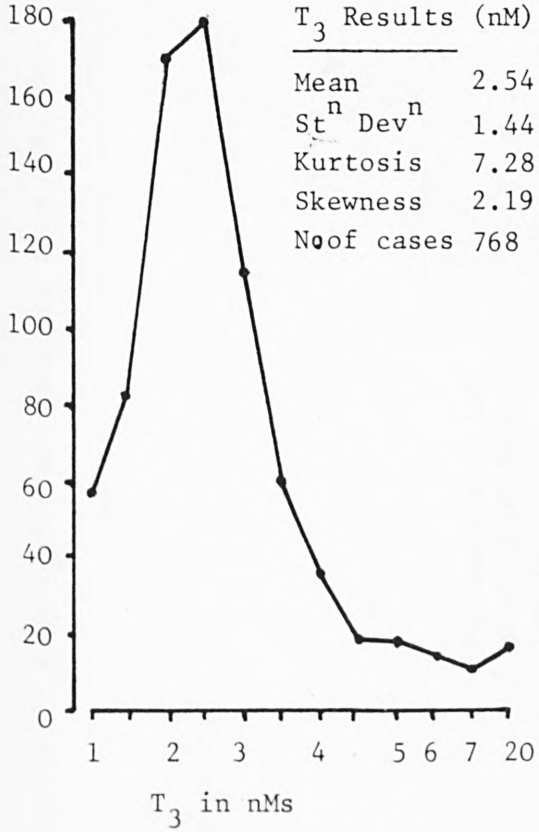
Distributions of FT_4I, T_3, and TSH results in J.N.Data

Figure 5.2

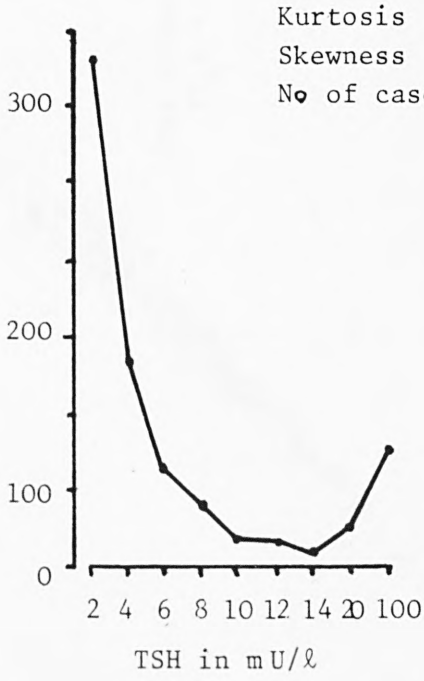
Frequency Polygons for FT_4I, T_3 and TSH Results in K.E.B. Data



FT_4I Results (nM)	
Mean	95.3 (±95% = 93-98)
St^n $Deviat^n$	48.5
Kurtosis	2.84
Skewness	1.31
No of cases	1316



T_3 Results (nM)	
Mean	2.54 (±95% = 2.4-2.6)
St^n Dev^n	1.44
Kurtosis	7.28
Skewness	2.19
No of cases	768

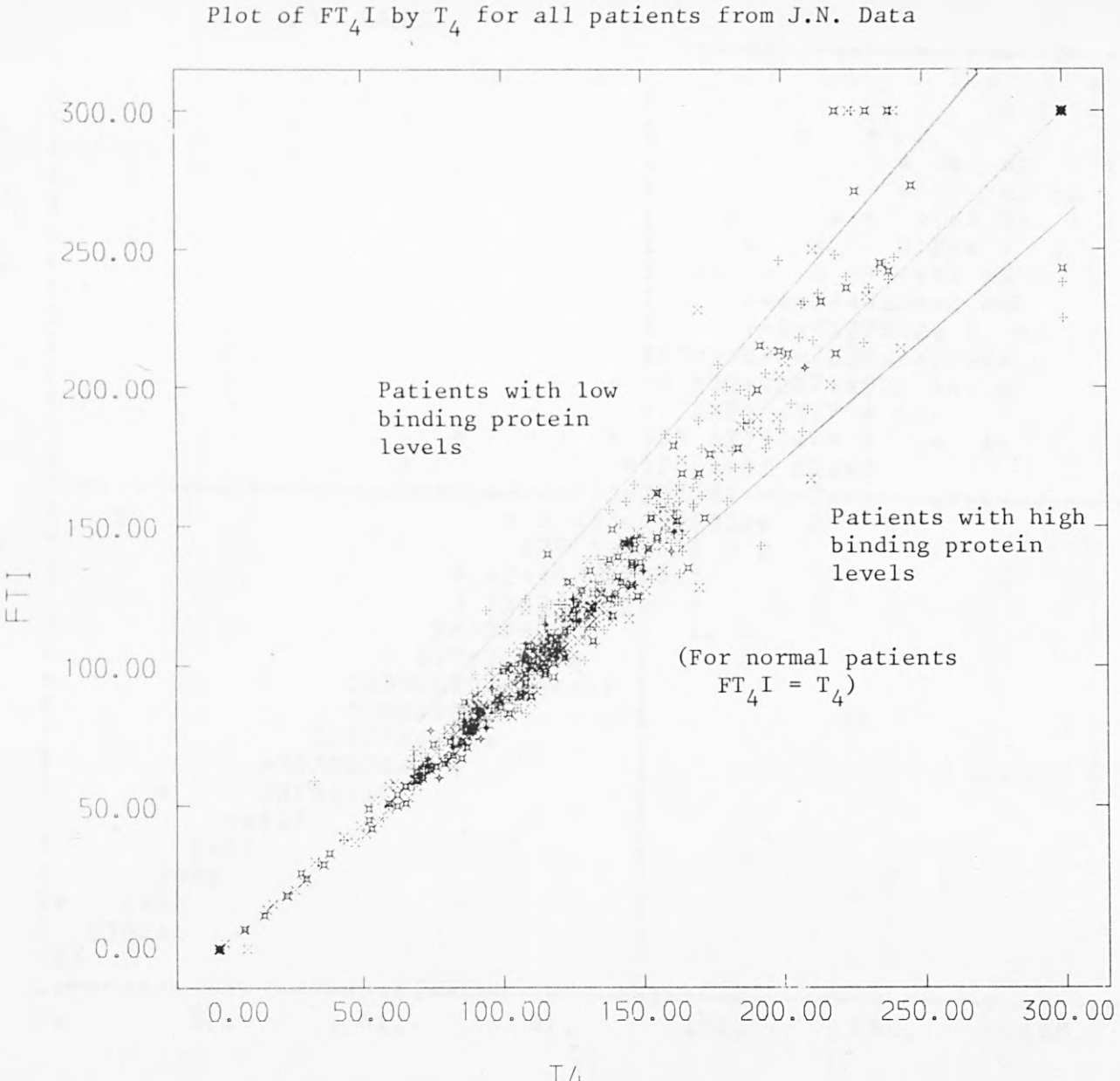


TSH Results (m U/ℓ)	
Mean	6.15
St^n Dev^n	8.57
Kurtosis	2.34
Skewness	1.90
No of cases	707

Note 95% confidence limits on means assume a Gaussian distribution

Distributions of FT_4I, T_3, and TSH results in K.E.B. Data

Figure 5.3



SYMBOL THERAPY

× NONE

+ ON T4

¤ CBZ

✧ PREG

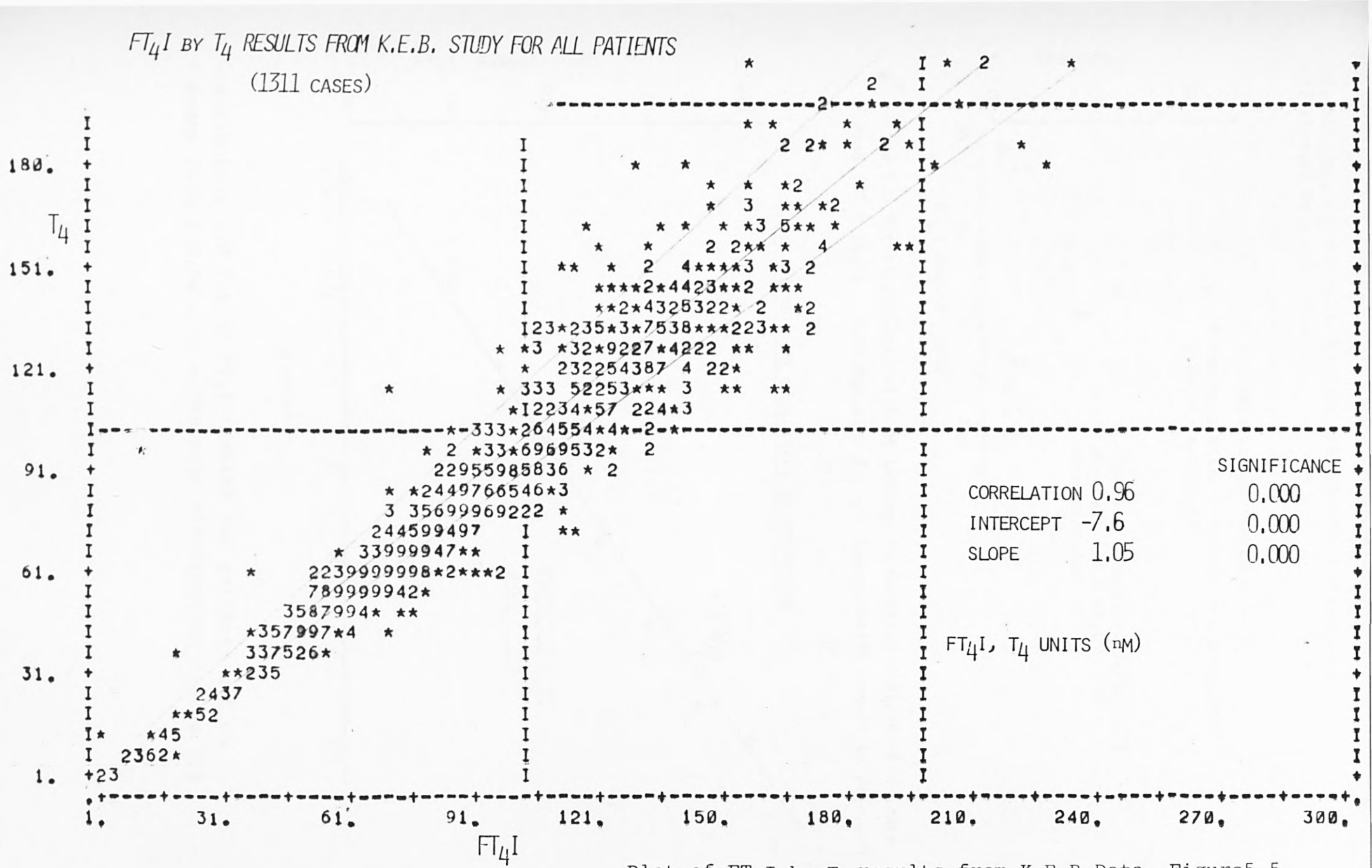
Lines show normal and ± 10% deviation

The measure of plasma thyroid hormone binding capacity used, the Resin T_3 uptake (RT_3U), is affected by T_4/T_3 concentration. This gives rise to the non-linearity seen in the figure.

Note PREG - Pregnant

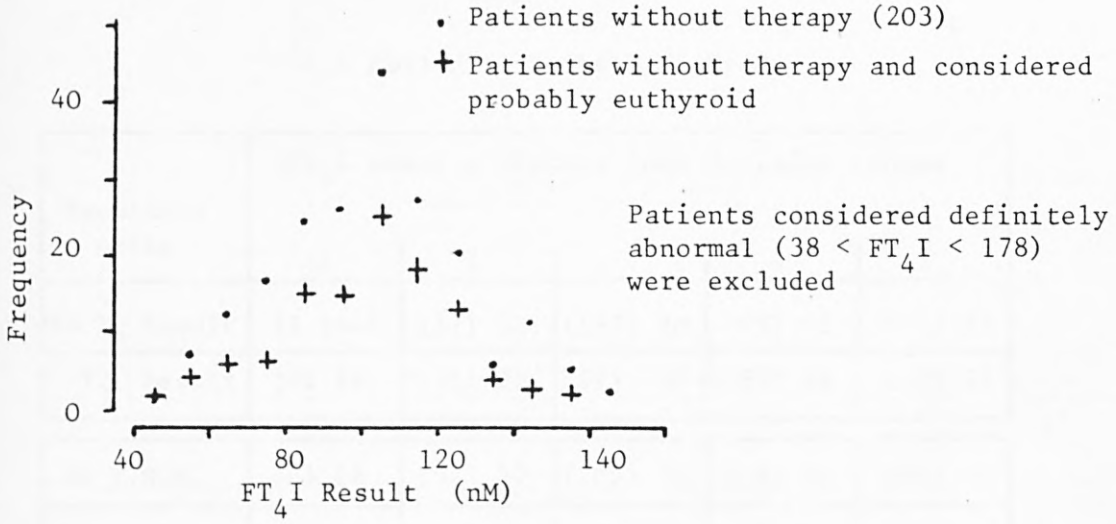
CBZ - Carbimazole

Figure 5.4

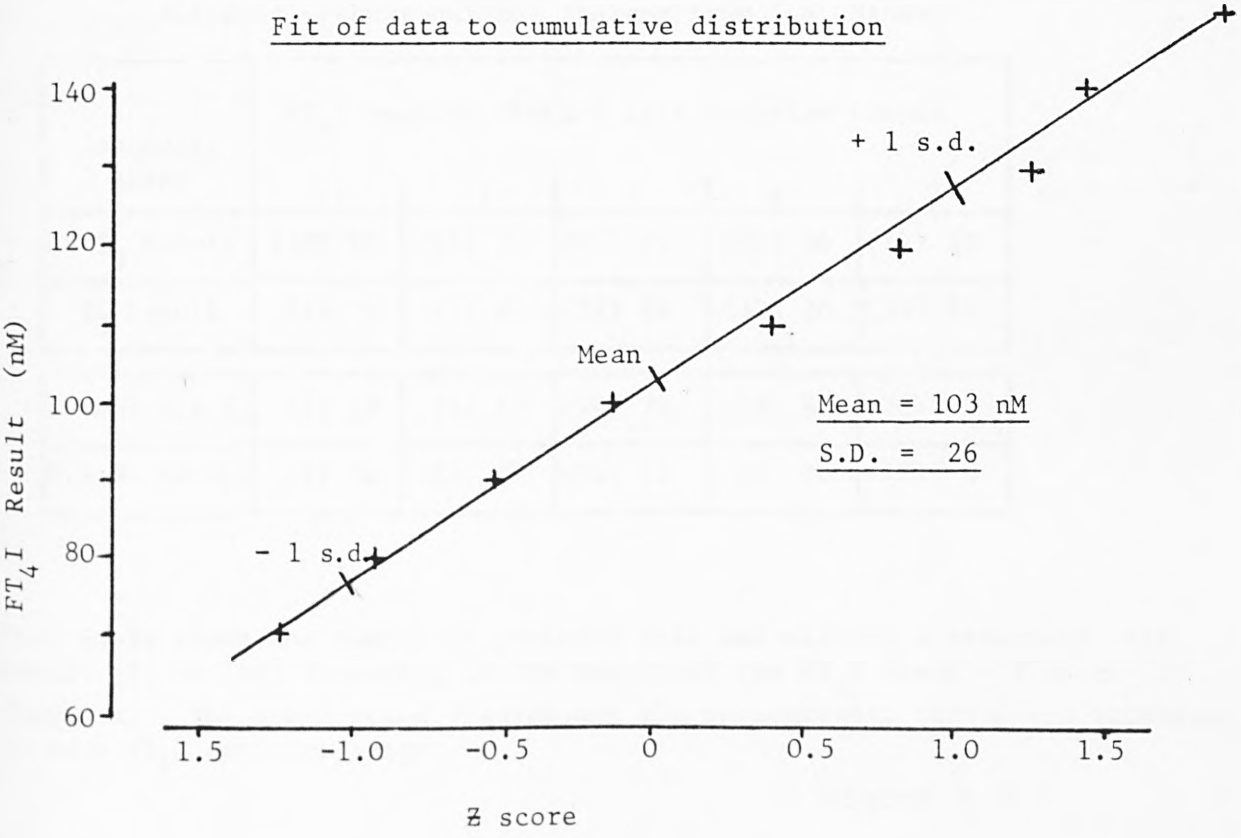


Plot of FT_4I by T_4 results from K.E.B.Data Figure5.5

Distribution and fit to a Gaussian distribution for patients off therapy from J.N. data



ψ^2 = 11.4 for fit of patients without therapy to Gaussian distribution where Prob (ψ^2 < 16.9) 0.05 for df = 9 ∴ Distribution cannot be rejected



Distribution and fit of FT_4I results for patients not on therapy from J.N.Data to a Gaussian distribution Figure 5.6

Dependence of Secondary Testing upon FT_4I Result

All Patients in the J.N. Study

Secondary Assay	FT_4I results divided into decision ranges				
	1	2	3	4	5
No T_3 Result	21 (84)	(67) 72	(187) 70	(95) 52	(52) 54
T_3 Result	(4) 16	(26) 28	(81) 30	(87) 48	(45) 46
No T.S.H.	(6) 24	(34) 37	(202) 75	(128) 70	(90) 93
T.S.H. Result	(19) 76	(59) 63	(66) 25	(54) 30	(7) 7

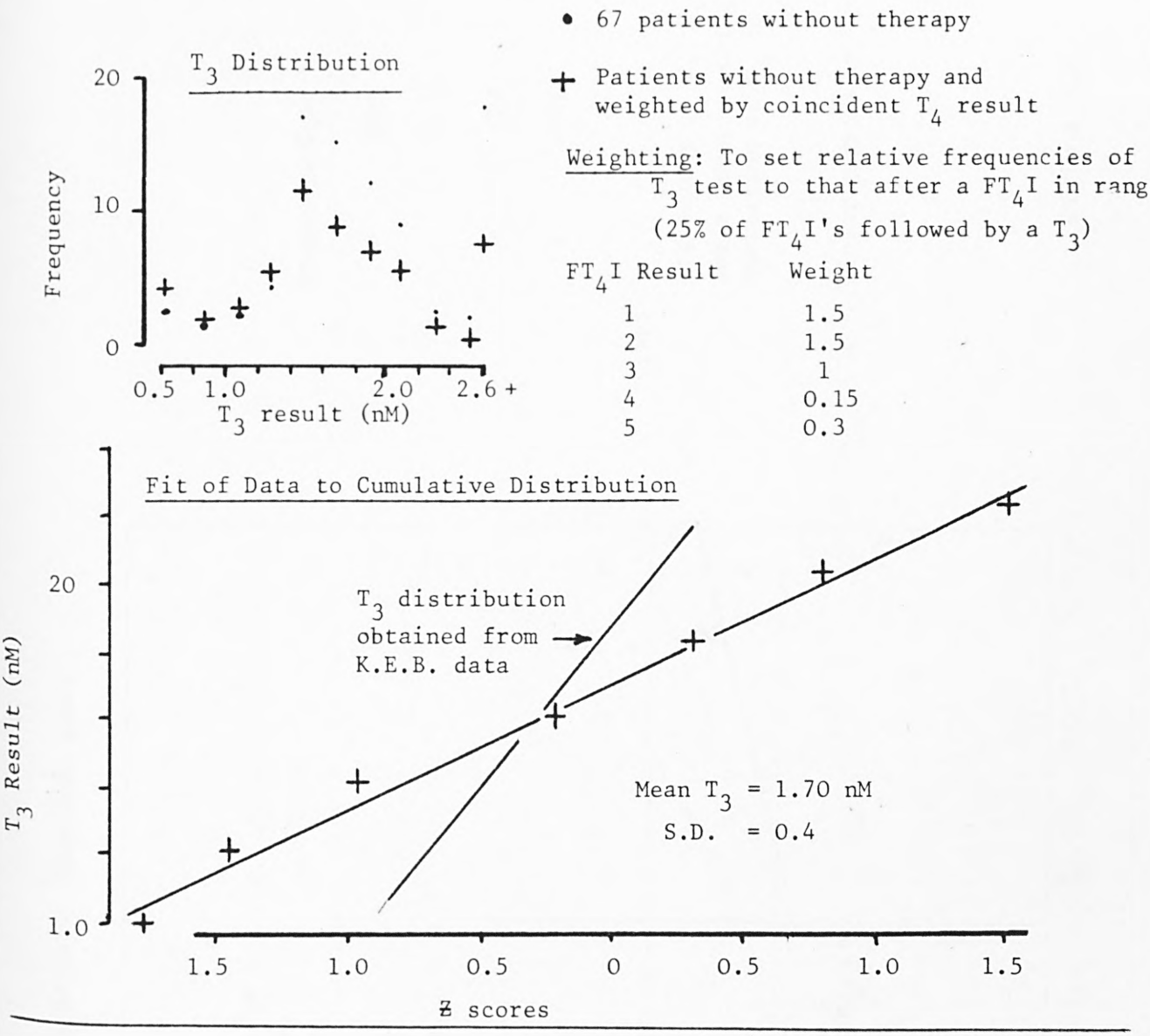
Patients without current therapy from J.N. Study

Secondary Assay	FT_4I results divided into decision ranges				
	1	2	3	4	5
No T_3 Result	(10) 91	(25) 78	(93) 74	(14) 30	(12) 48
T_3 Result	(1) 9	(7) 22	(32) 26	(32) 70	(13) 52
No T.S.H.	(2) 18	(4) 13	(99) 79	(38) 82	(23) 92
T.S.H. Result	(9) 82	(28) 87	(26) 21	(8) 18	(2) 8

Each table shows the number of patients with and without a secondary test result (T_3 or TSH) according to the result of the FT_4I assay - figures in brackets. The unbracketed figures are the percentages, tested and untested, in each FT_4I decision range.

Figure 5.7

Distributions of T_3 and TSH results from patients without therapy from J.N. data



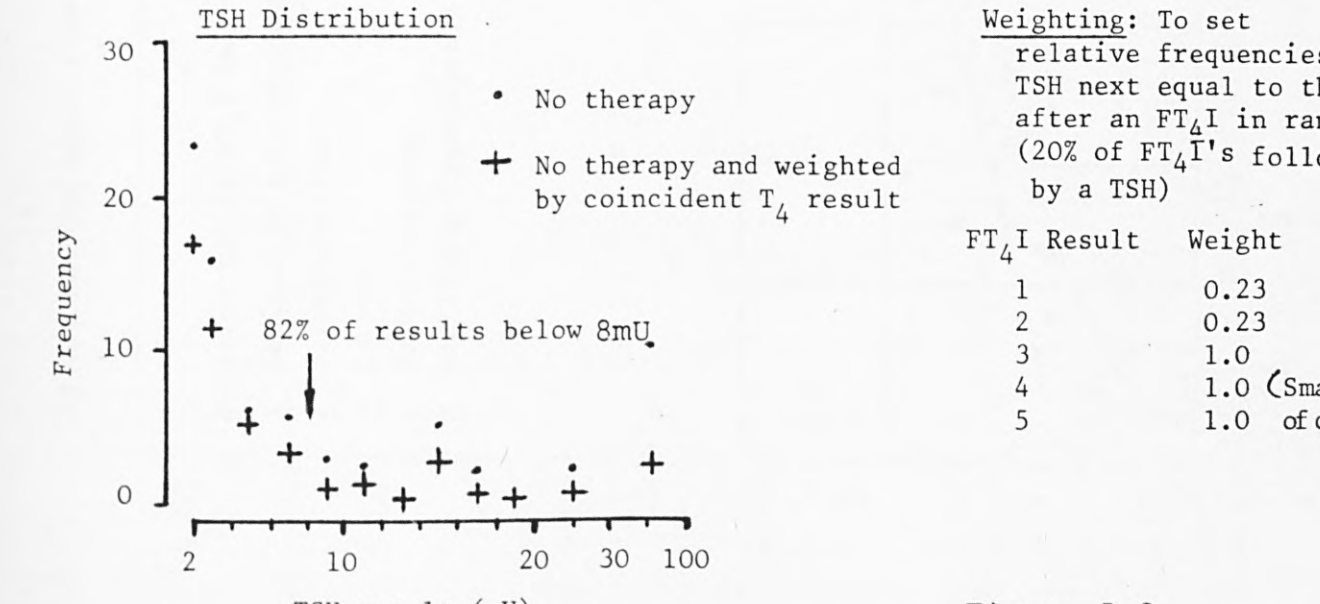
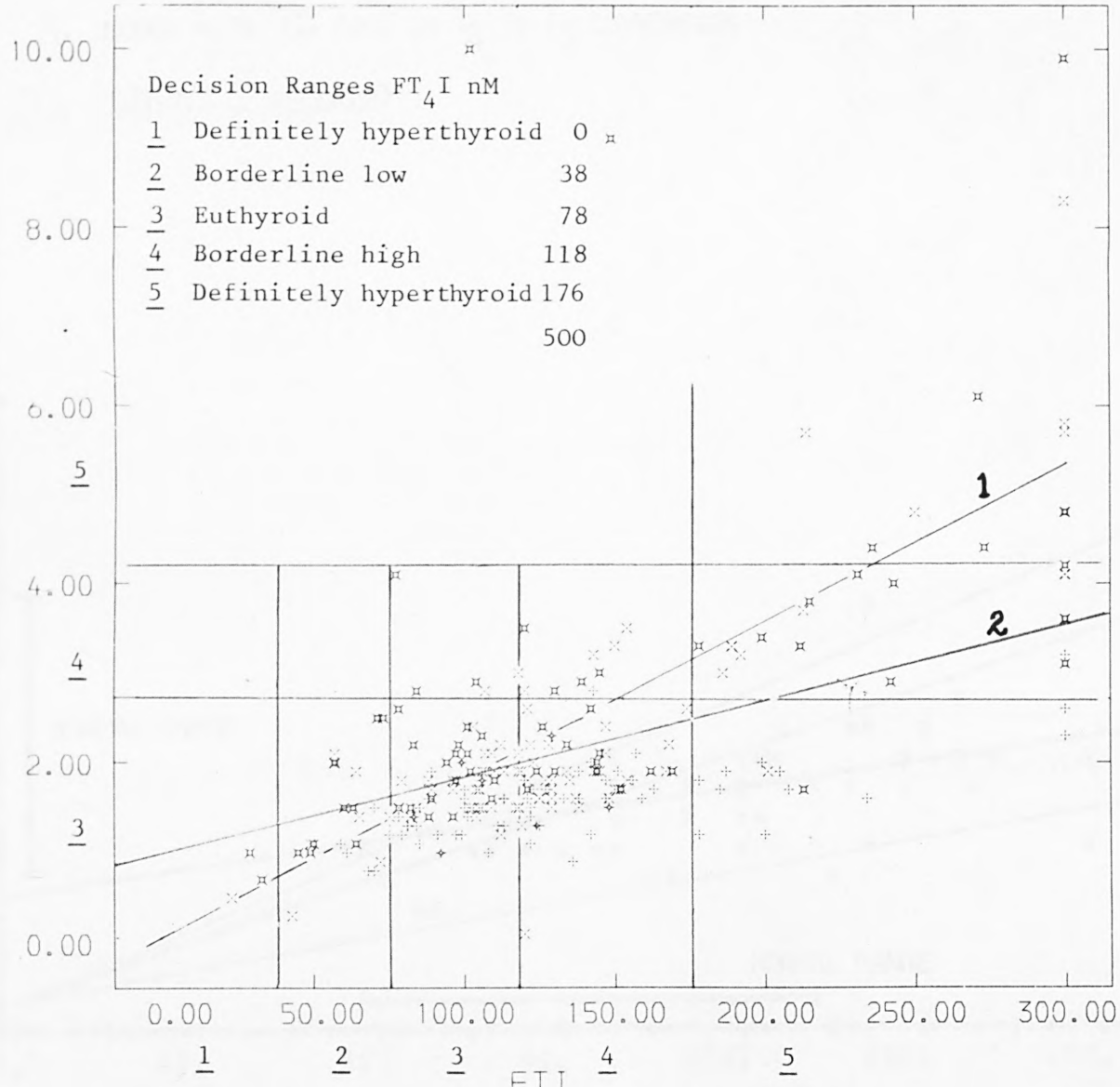


Figure 5.8

Thyroid hormone space showing patients from J.N. study



SYMBOL THERAPY

× NONE

+ ON T4

¤ CBZ

◆ PREG

Lines

1 Trajectory of T_3, T_4 changes for a model assuming linear conversion of T_4 to T_3.

2 Linear regression on all patients

Figure 5.9

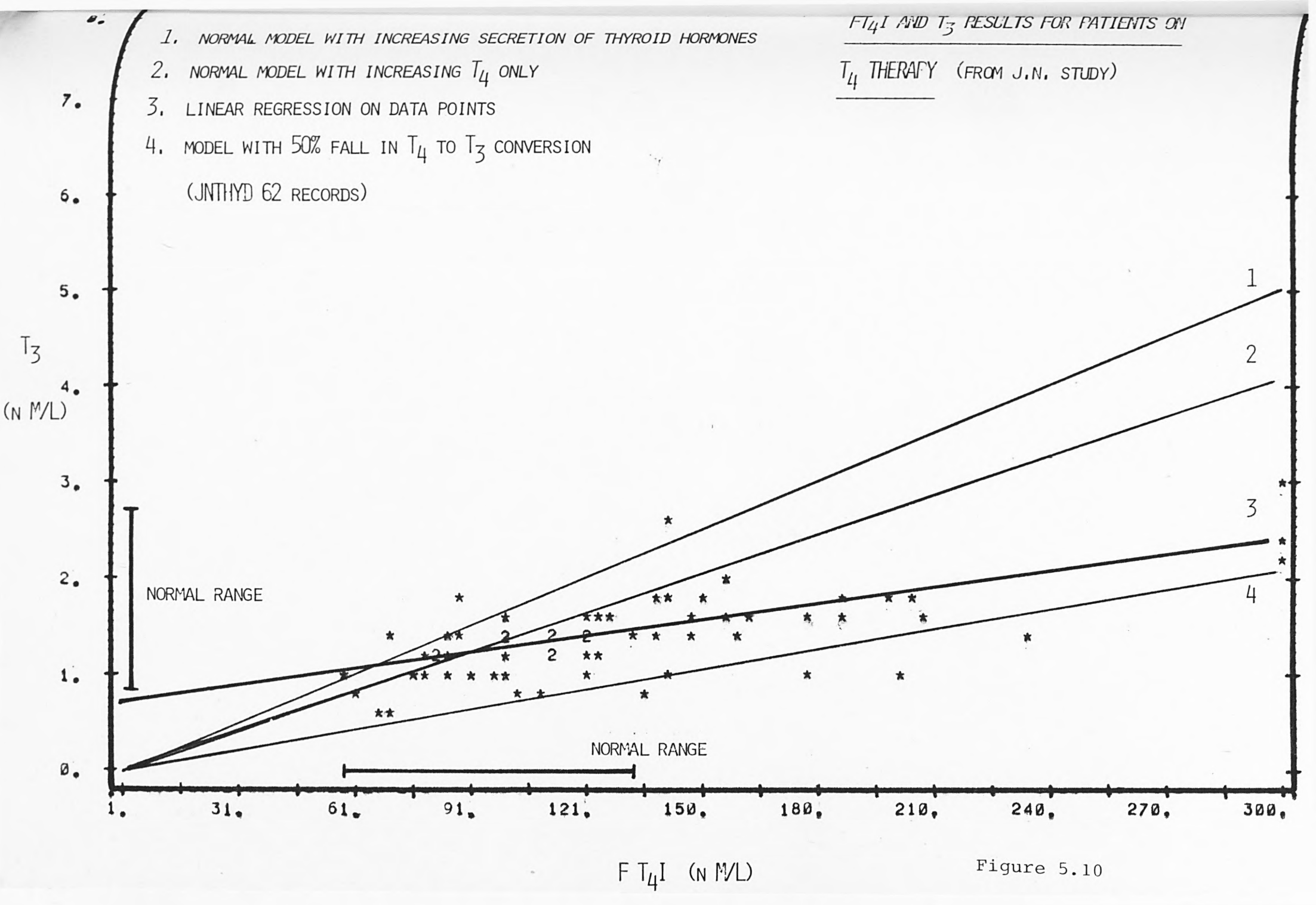

1. NORMAL MODEL WITH INCREASING SECRETION OF THYROID HORMONES
2. NORMAL MODEL WITH INCREASING T_4 ONLY
3. LINEAR REGRESSION ON DATA POINTS
4. MODEL WITH 50% FALL IN T_4 TO T_3 CONVERSION
(JNTHYD 62 RECORDS)
FT_4I AND T_3 RESULTS FOR PATIENTS ON T_4 THERAPY (FROM J.N. STUDY)
T_3 (N M/L)
7.
6.
5.
4.
3.
2.
1.
0.
NORMAL RANGE
NORMAL RANGE
1
2
3
4
1.
31.
61.
91.
121.
150.
180.
210.
240.
270.
300.
F T_4I (N M/L)

Figure 5.10

1. NORMAL MODEL WITH INCREASING SECRETION OF T.H.'S
2. NORMAL MODEL WITH INCREASING T_4 ONLY
3. LINEAR REGRESSION ON DATAPOINTS
4. 50% FALL IN CONVERSION OF T_4 TO T_3

(KBTHYD 83 RECORDS)

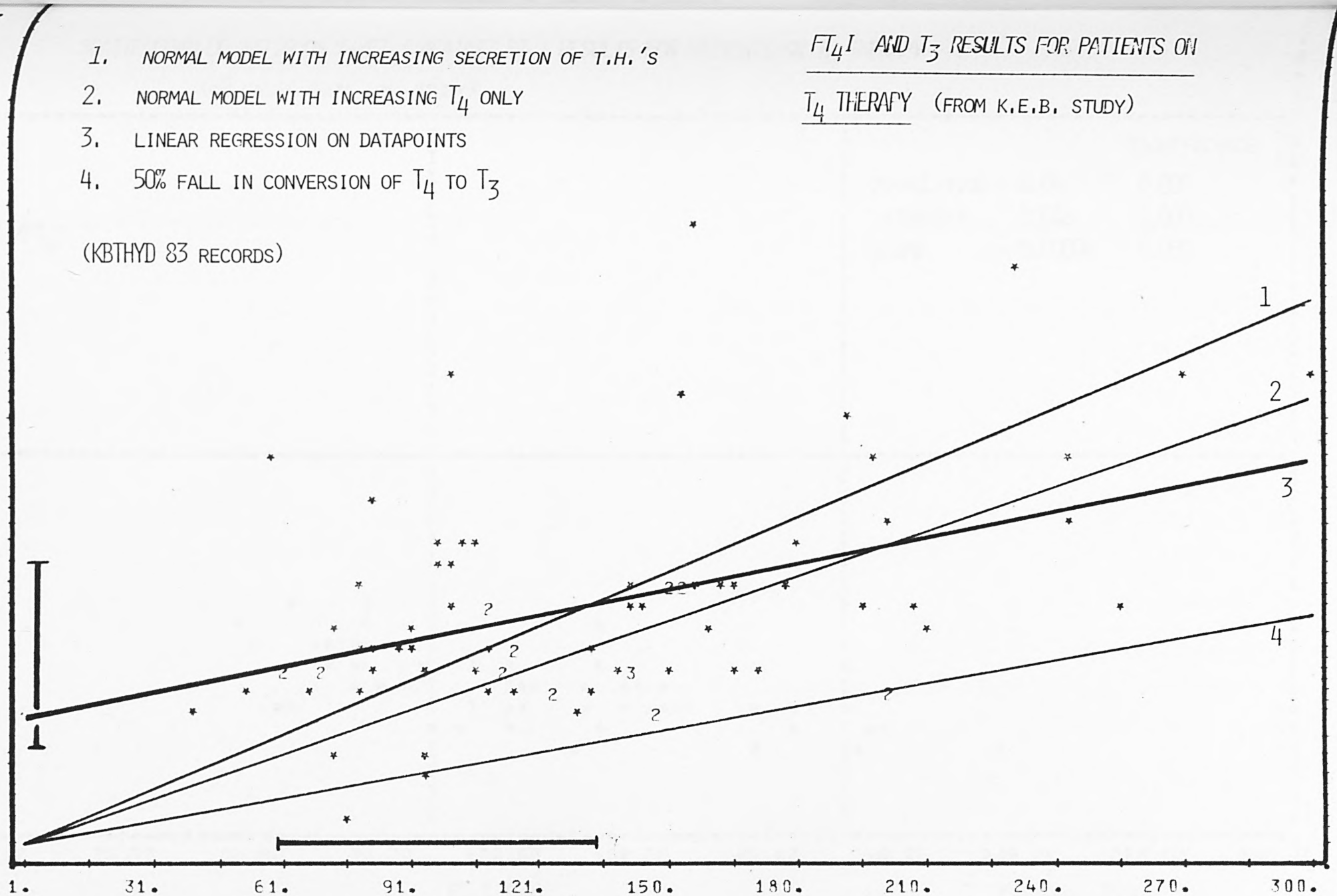


Figure 5.11

SCATTERGRAM OF RATIO OF T_3/FT_4I AGAINST FT_4I RESULTS FOR PATIENTS ON T_4 THERAPY

(62 CASES FROM J.N. STUDY)

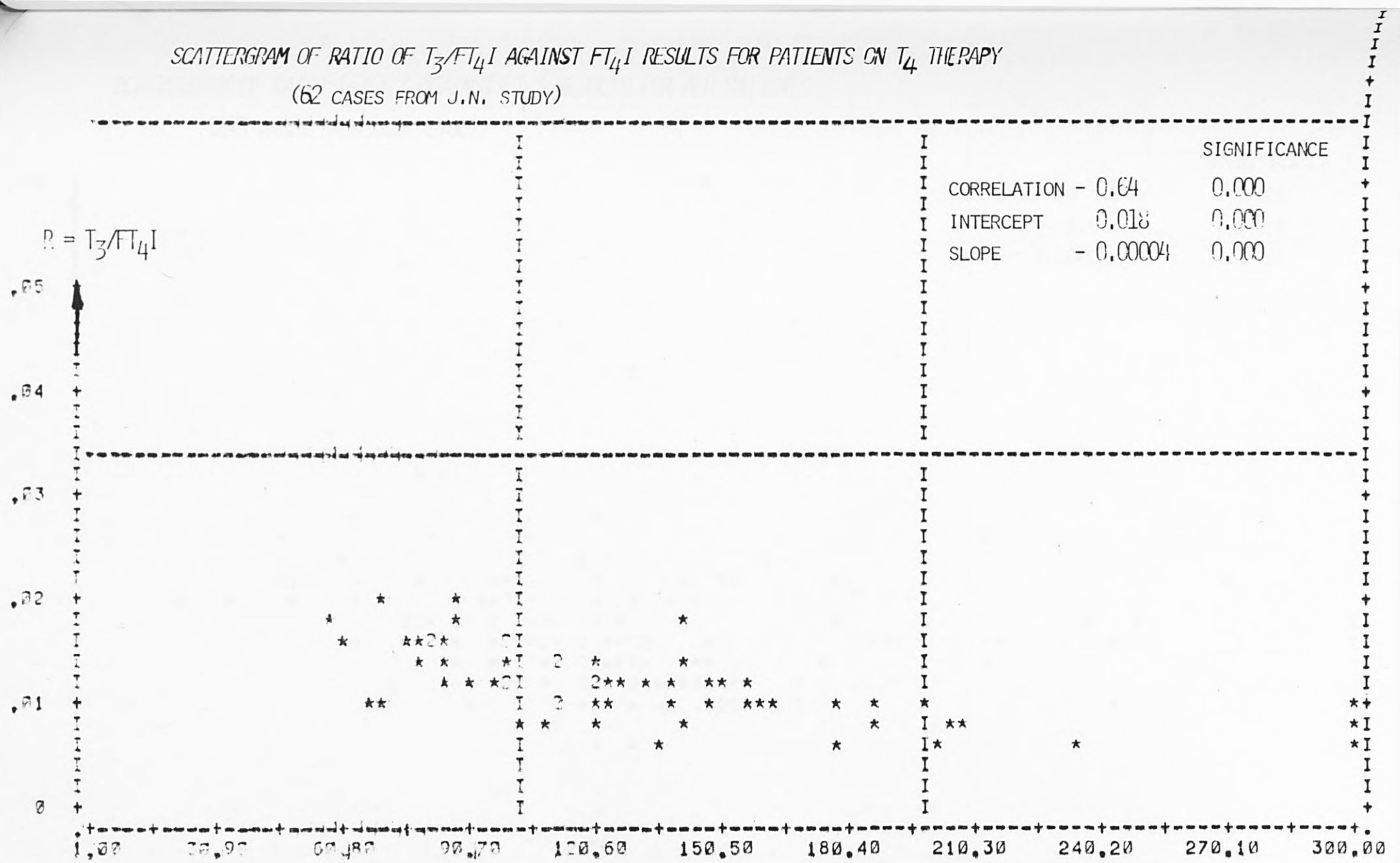


Figure 5.12

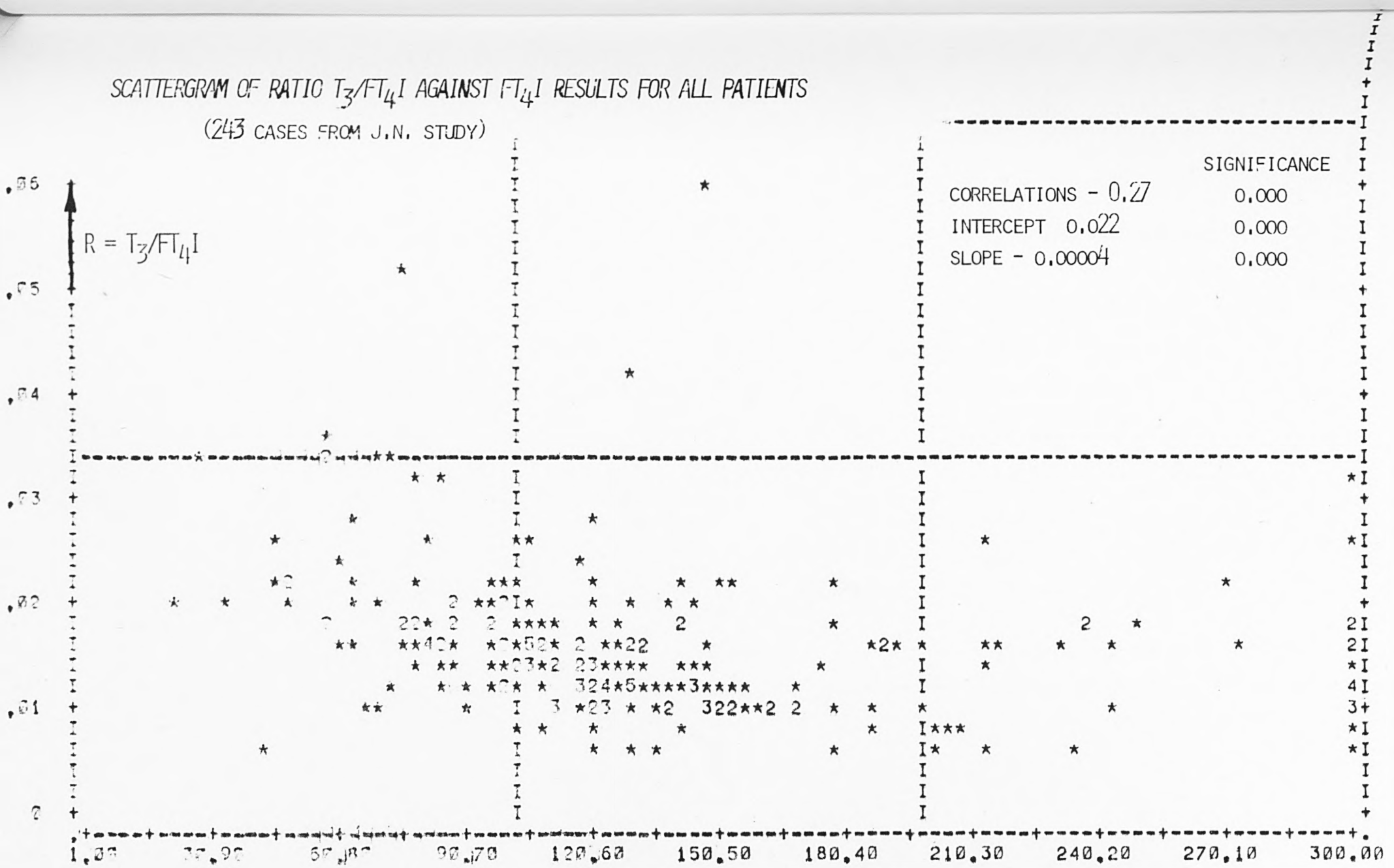

SCATTERGRAM OF RATIO T_3/FT_4I AGAINST FT_4I RESULTS FOR ALL PATIENTS
(243 CASES FROM J.N. STUDY)
R = T_3/FT_4I
SIGNIFICANCE
CORRELATIONS - 0.27 0.000
INTERCEPT 0.022 0.000
SLOPE - 0.00004 0.000
.06
.05
.04
.03
.02
.01
0
1.00
30.90
60.80
90.70
120.60
150.50
180.40
210.30
240.20
270.10
300.00
FT_4I (nM)

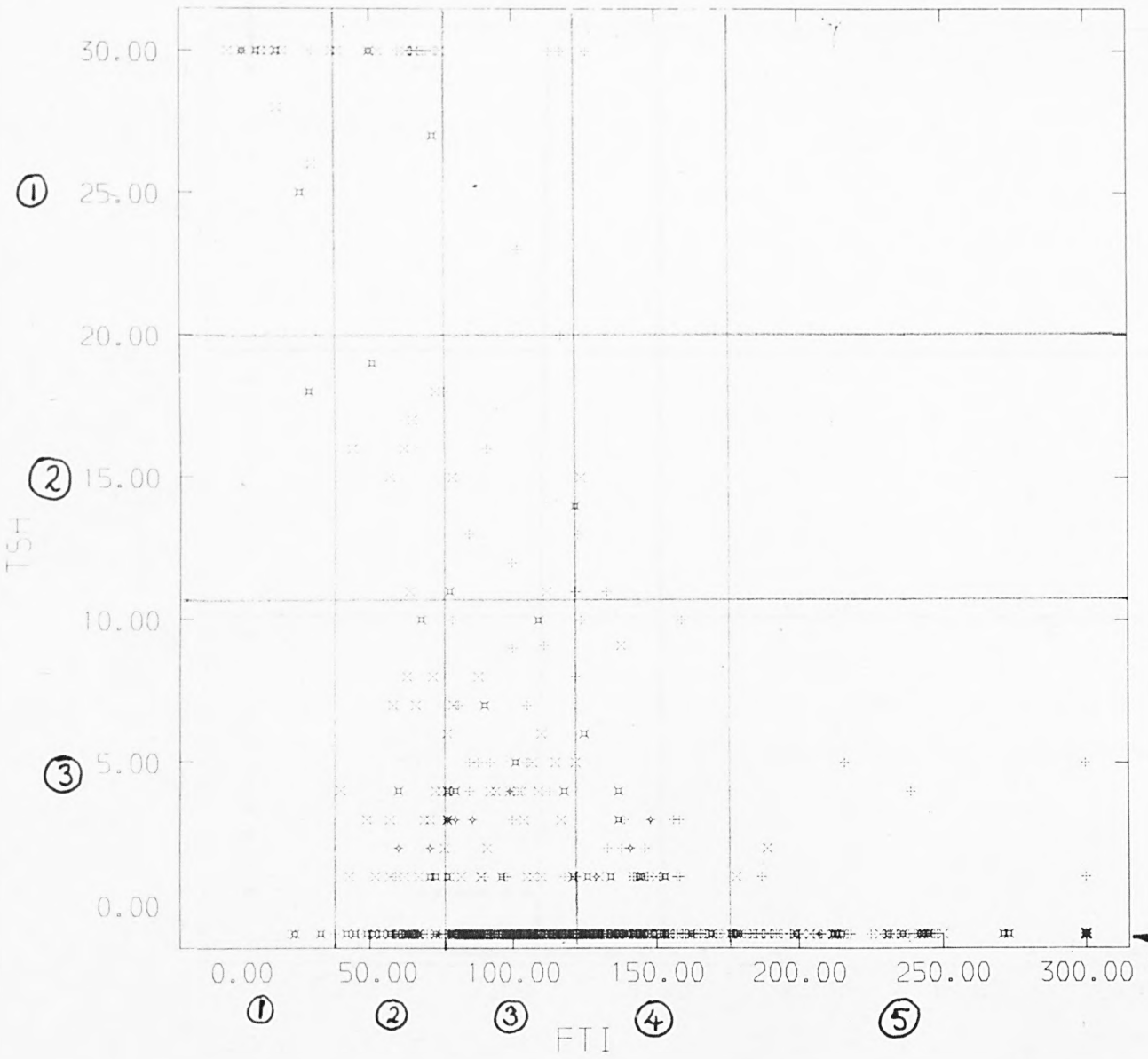
Figure 5.13

Free Thyroxine Index and Thyrotropin results divided into decision ranges

(171 cases from the J.N. Study)

FTI results in nM

TSH results in mU



SYMBOL	THERAPY
×	NONE
+	ON T4
¤	CBZ
✧	PREG

1 Definitely hypothyroid
2 Borderline low
3 Euthyroid
4 Borderline high
5 Definitely hyperthyroid

FTI Results with no TSH data

Figure 5.14

Triiodothyronine (T_3) by Thyrotrophin (TSH) results

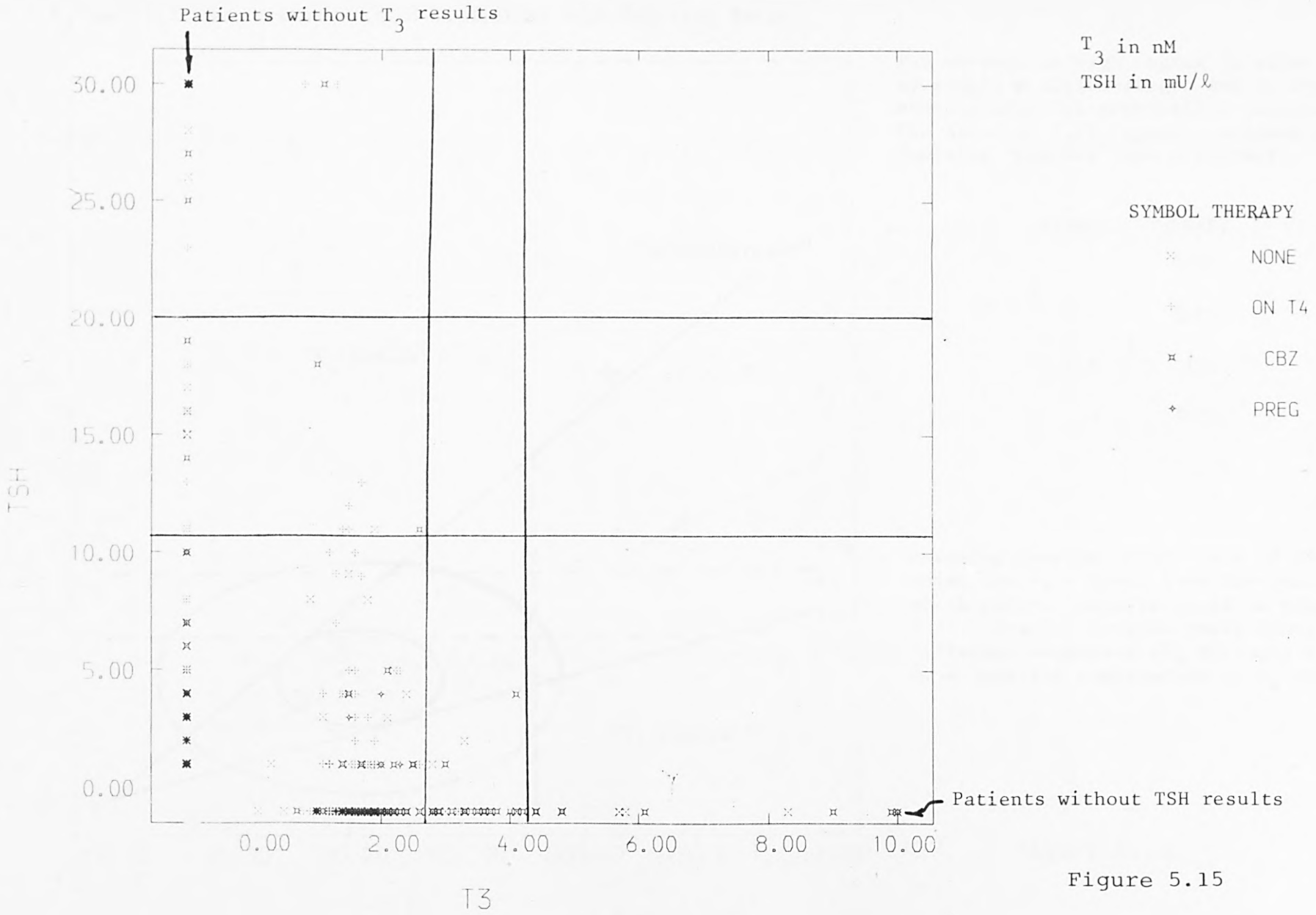
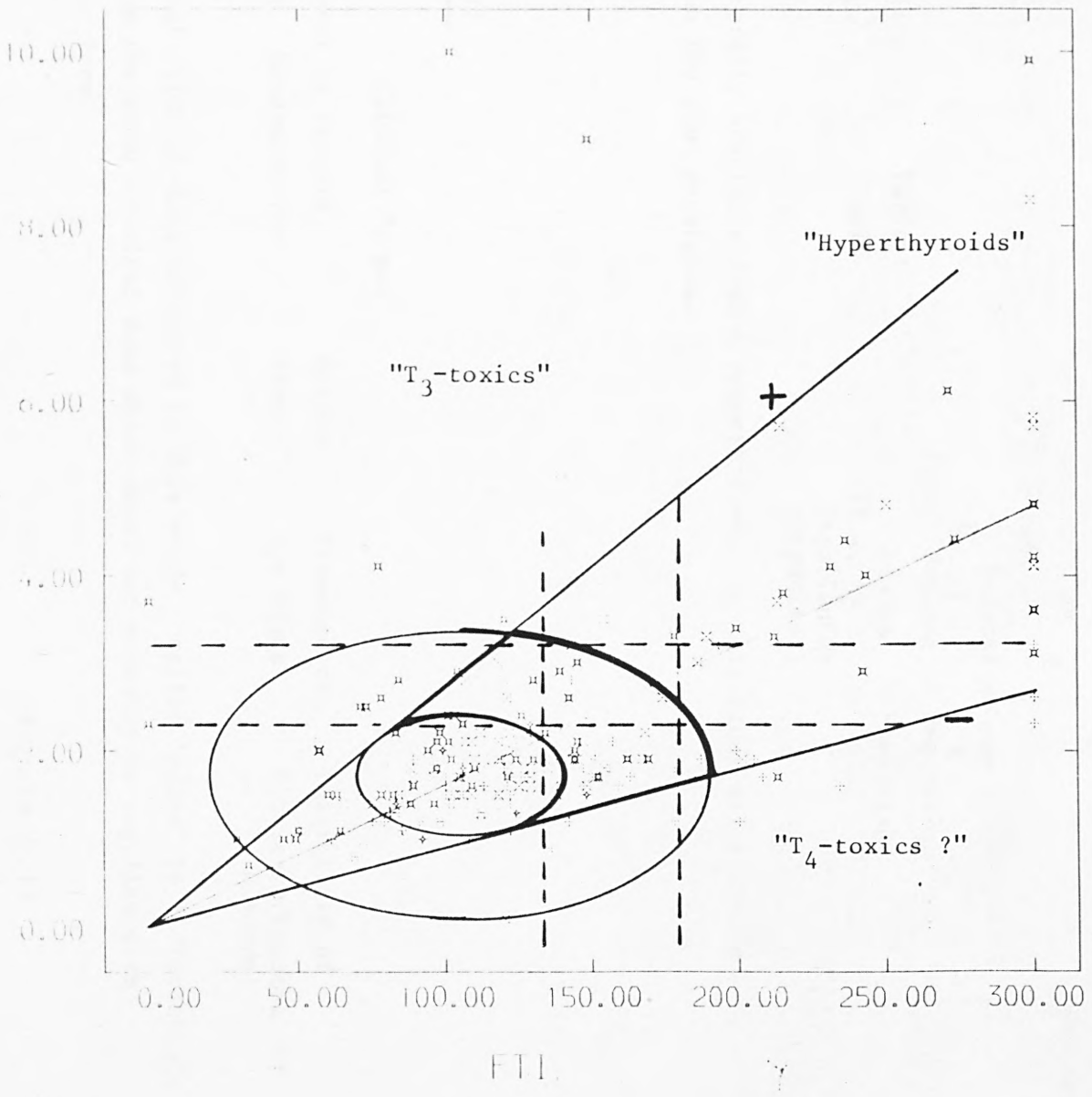


Figure 5.15

T_3 and FT_4I Space with Modified Borderline High Decision Range



The borderline high region is shown divided by simple decision-ranges and by the more exact elliptical probability contains. The areas of T_3/T_4 space, enclosed in the decision 'regions' are different.

SYMBOL	THERAPY
×	NONE
+	ON T4
¤	CBZ
◇	PREG

Assuming constant proportion of measurement noise the +, - lines show the region in which patient results could be expected to fall. Results outside these lines suggest different responses (T_4 therapy, T_3 toxics) or a doubtful combination of T_4 and T_3 results

Figure 5.16

Breakdown of Clinical Variables Obtained in J.N. Study

Group I

Overall Clinical Assessment	Current Drug Therapy	Previous Thyroid/Pituitary therapy

Basic data which should be supplied with an assay request if the assay service is to take any interpretative action on assay result

Group II

Patient Age	Patient Sex	Request source / Patient Status (i.e. inpatient or outpatient)	Request source \ Requesting Physician

Data generally available from a request form. In this study all requests come from the same physician.

Group III

Clinical "signs"

Result of Thyroid Antibody Determination	Goitre Status	Presence of Eye Signs	Possibility of Pituitary/Hypothalmic Disorder

Additional clinical data collected in this study - called 'signs' to differentiate them from the other clinical data which would not normally be supplied with a request form

Figure 5.17

Distribution of Clinical Variables in J.N. Data

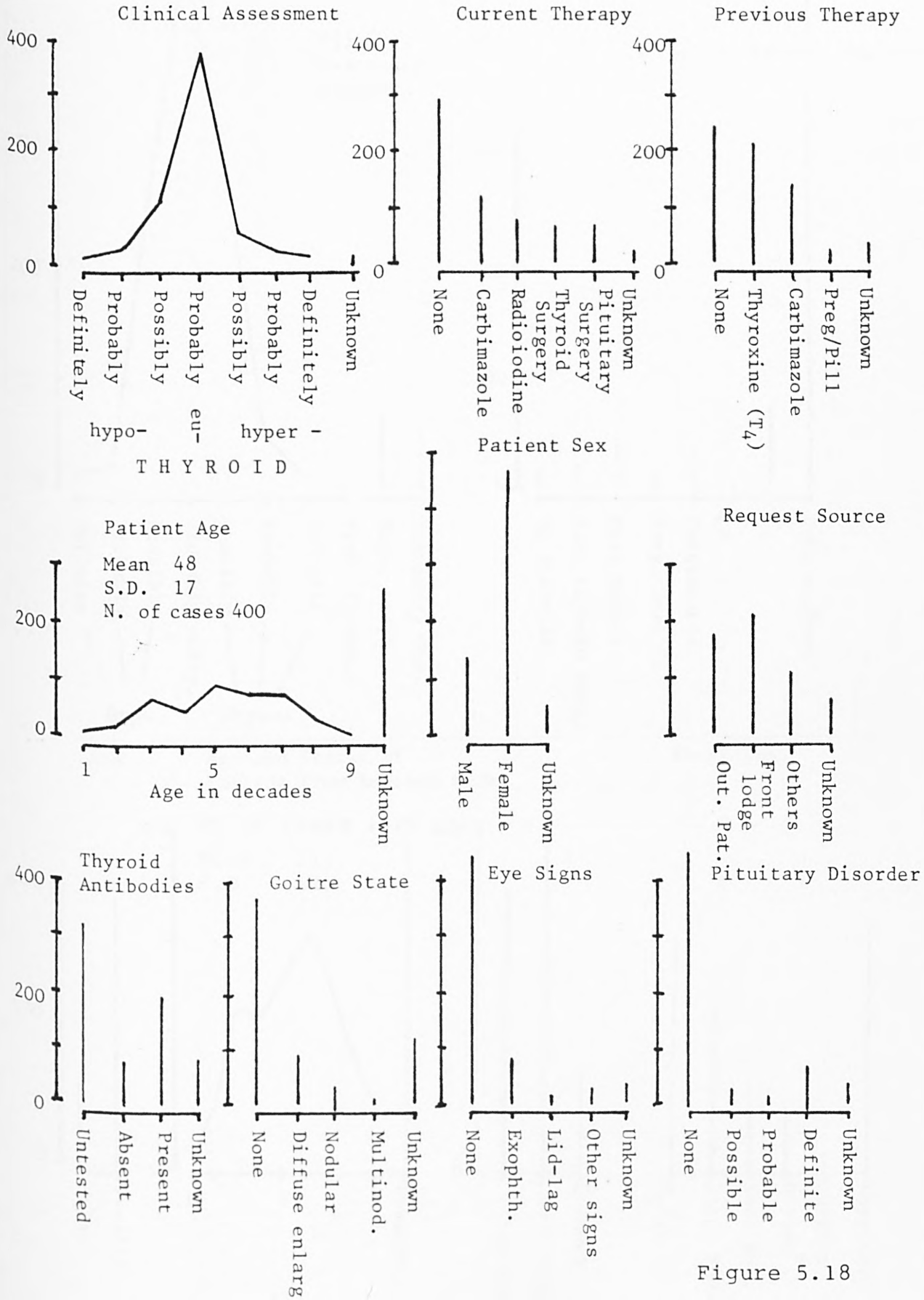


Figure 5.18

Frequencies of Clinical Data in K.E.B. Study

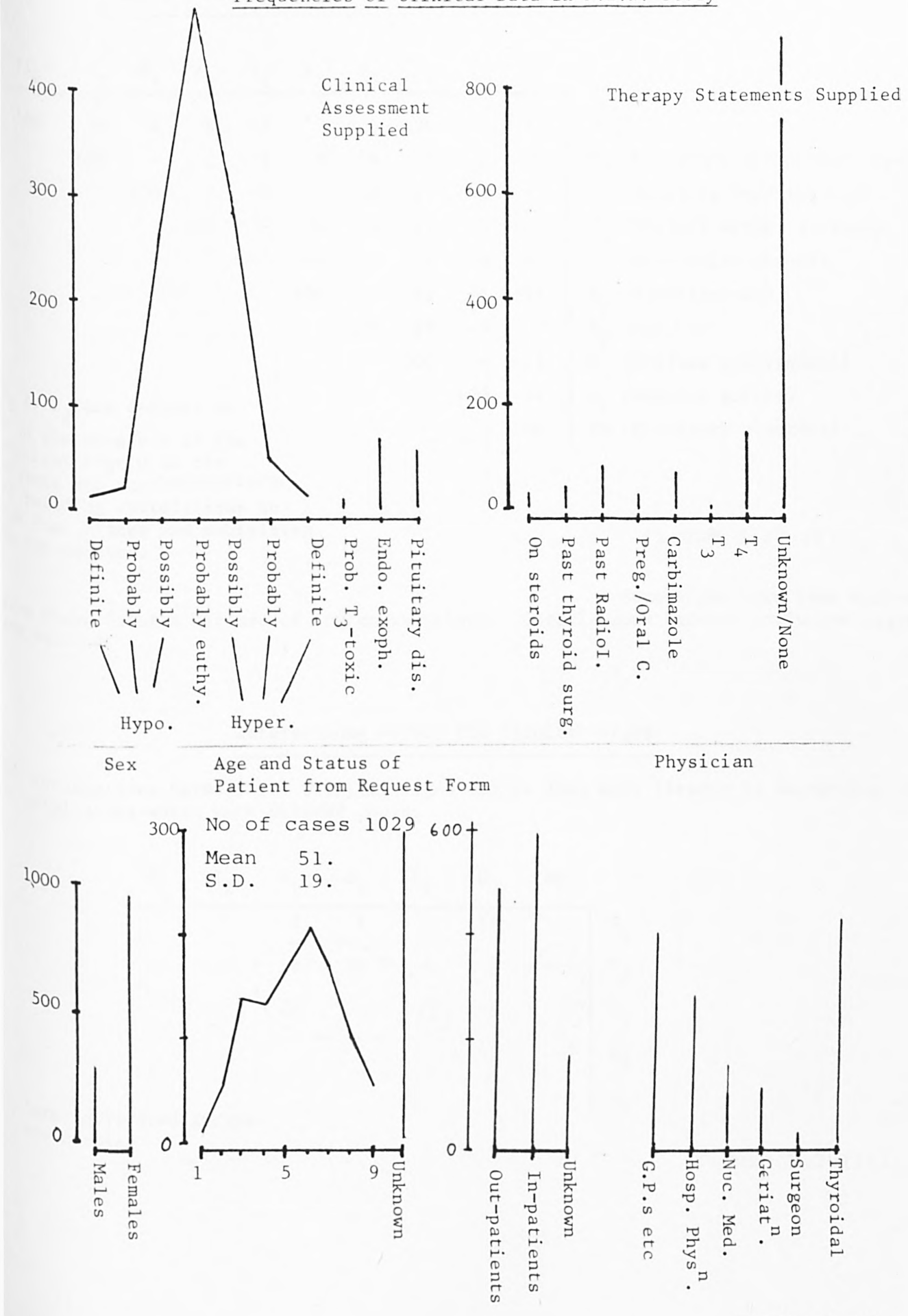


Figure 5.19

Simple Correlations Obtained Between FT_4I and Clinical Variables

FT_4I	C_5	C_4	T_2	T_1	E_1	E_2	G_1	G_2	PD	
100	35	6	6	-3	7	16	20	-5	-6	FT_4I
	100	-	2	-2	8	26	28	2	-9	C_5 (Probably or definitely hyper.)
		100	7	-1	7	10	17	-3	-7	C_4 (Possibly hyperthyroid)
			100	-	19	4	19	4	-25	T_2 (Thyroid antib. present)
				100	-3	6	1	14	-1	T_1 (Antibodies absent)
					100	-	21	-5	-15	E_1 (Exophthalmos)
						100	18	-3	7	E_2 (Lid lag)
							100	-	-13	G_1 (Diffuse enlargement)
								100	-9	G_2 (Nodular goitre)
									100	PD (Pituitary disorder)

C_5 to G_2 are defined as 1 in the presence of the clinical sign, 0 in the absence and the convention of rounding correlations to two dec. places and multiplying by 100 adopted.

Figure 5.20 (i)

Some signs have been excluded from these figures because of low correlations. Correlations between exclusive signs are omitted.

Interactions Within the Clinical Signs

The interactions between the clinical signs can be seen more clearly by reordering the clinical signs which were defined above.

T_1	T_2	E_1	G_1	E_2	G_2	PD	
		-3	1	6	14	-1	T_1
		19	19	4	4	-25	T_2
		21		18	-5	-13	G_1
					-2	-7	E_2
						-9	G_2

Intercorrelated groups are circled

Figure 5.20(ii)

Crosstabulations of Goitre Signs, Eye Signs and Antibody Results in J.N. Data

Male

Thyroid Antibodies	Goitre State: None	Diffuse	Nodular	Multinod.
Unknown	57	1	1	0
Absent	9	0	0	1
Present	28	8	2	0

Female

Goitre State: None	Diffuse	Nodular	Multinod.	Neoplas.
142	31	5	4	1
30	10	9	2	0
69	33	5	1	0

Thyroid Antibodies	Eye Signs: None	Exophth.	Lid Lag	Other
Unknown	63	2	1	1
Absent	10	0	1	1
Present	21	13	3	3

Eye Signs: None	Exophth.	Lid Lag	Other
183	19	5	6
46	7	3	3
94	23	4	7

Eye Signs	Goitre State: None	Diffuse	Nodular	Multinod.
None	78	3	2	1
Exophth.	10	4	0	0
Lid lag	4	1	0	0
Other	2	1	1	0

Goitre State: None	Diffuse	Nodular	Multinod.	Neoplas.
209	40	18	7	1
25	19	0	0	0
4	9	0	0	0
4	6	1	0	0

(Clinical signs are detailed on Request Forms and there were no male cases of neoplasia)

Figure 5.21

Frequencies of Clinical Signs by Patient Age and Sex

MALES

Age	1	2	3	All
1	2 8	0 0	0 0	25
2	4 10	1 2	0 0	39
3	0 0	1 7	0 0	14

FEMALES

1	2	3	All
24 28	2 2	3 3.5	86
17 17	8 8	1 1	98
9 12	2 3.6	1 1.3	77

← Goitre Status

1. Diffuse goitre
2. Single nodule
3. Multinodular

← Absolute frequency
← % of patients of each age

Age	1	2	3	All
1	3 10	0 0	4 14	29
2	7 18	2 5	3 8	39
3	12 12	12 12	0 0	16

1	2	3	All
18 20	2 2	0 0	92
14 13	4 4	5 5	104
6 7	4 4.5	2 3	89

← Eye Signs

1. Exophthalmos
2. Lid lag
3. Other eye signs

	1	2	3	All
1	7 23	4 13	4 13	31
2	3 7	3 7	8 19	43
3	0 0	1 6	6 38	16

1	2	3	All
9 10	1 1	10 11	93
2 2	3 3	5 4.5	111
3 3	2 2	1 1	90

← Pituitary Disorder

1. Possible
2. Probable
3. Definite

	1	2	All
1	0 0 0	7 23 100	31 100
2	5 12 30	12 28 70	43 100
3	1 6 17	5 31 83	16 100

1	2	All
9 10 33	18 19 67	93 100
12 11 32	26 23 68	111 100
11 12 29	27 30 71	90 100

← Thyroid Antibodies

1. Absent
2. Present

— Absolute frequency
— % of patients of each age
— % of patients tested/age

Frequency of Patients in each age group

Age groups (1 = 0 to 40)(2 = 41 to 60 (3 = 61 to 100)

Figure 5.22

Dependence of Clinical Assessment upon Other Clinical Data

The very large differences between the occurrences of the clinical assessments tends to obscure the effects of other clinical data. The relative differences from the modes have therefore been plotted here to show how different values affect the distribution of assessments.

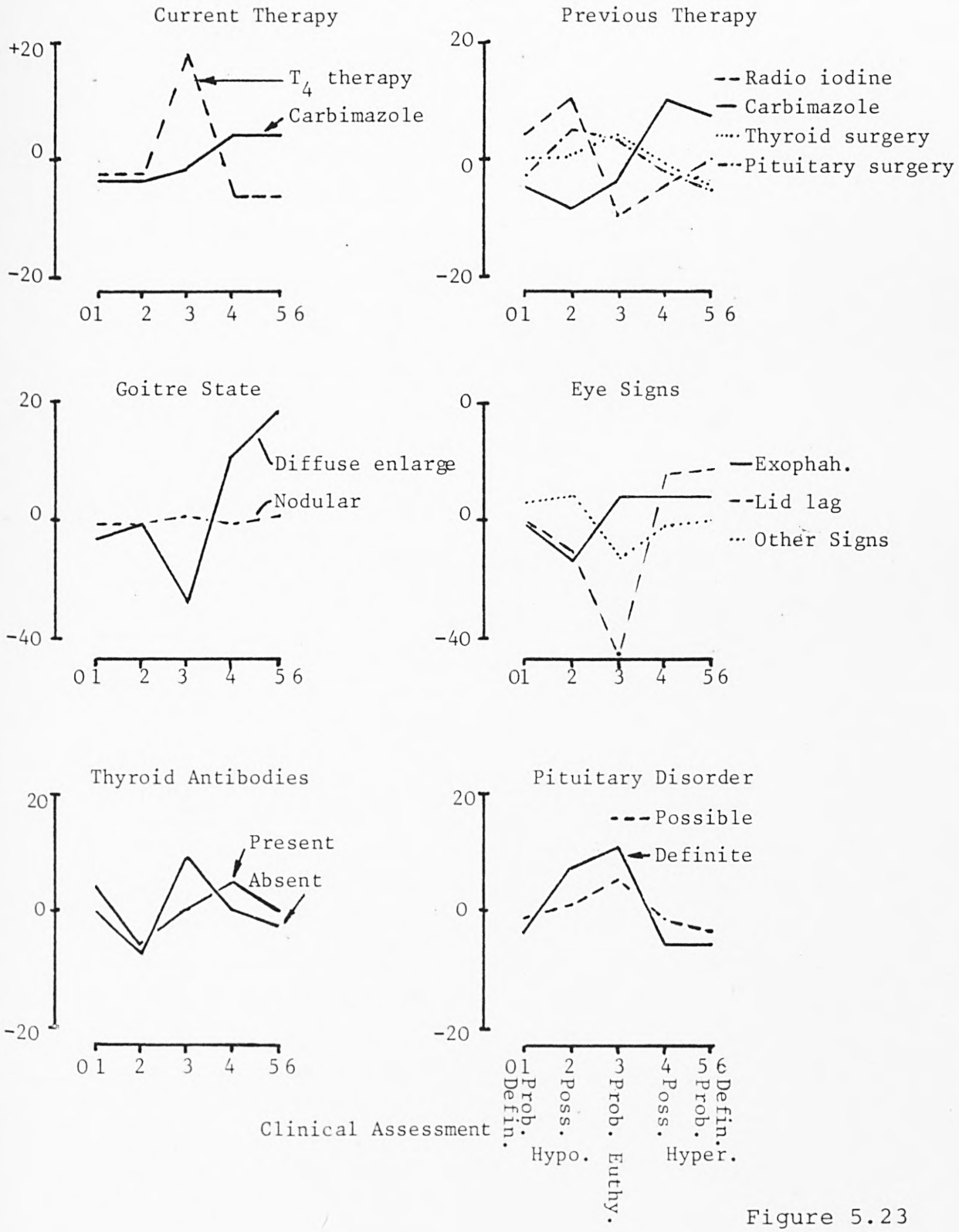


Figure 5.23

Linear Regression of Clinical Signs on the Physician's Clinical Assessment

Clinical Sign	R^2 Change	Significance	
Current Therapy			
T_4	0.007	0.085	
Carbimazole	0.004	0.451	
Previous Therapy			
Carbimazole	0.008	0.016	
Radio. Iodine	0.035	0.000	*
Thyroid Surgery	0.005	0.074	
Pituitary Surgery	0.002	0.926	
Thyroid Antibodies			
Present	0.000	0.002	
Absent	0.002	0.392	
Goitre Signs			
Diffuse Enlarged	0.041	0.000	*
Nodular	0.000	0.380	
Multinodular	0.001	0.663	
Eye Signs			
	0.018	0.001	*
Lid Lag	0.050	0.000	*
Other Signs	0.008	0.058	
Pituitary			
Disorder	0.006	0.026	
Male	0.001	0.081	

With all clinical signs included

Multiple R = 0.431

R^2 = 0.186

Adjusted R^2 = 0.166

* Signs with significance greater than 1%

Figure 5.24

Linear Discrimination of Clinical Assessment by Other Clinical Data

The discriminator seeks to maximise distances between classes defined by the clinical assessment in discriminant space. Variables are added to the discriminant function in sequence.

Significantly discriminative variables from J.N. Data (669 cases)

Variable	Δ in Rao's V	Significance
Diffuse goitre	108.0	0.000
T. Antis. Present	14.2	0.028
Previous Cbz.	22.4	0.001
Lid lag	65.8	0.000
Current T_4	18.2	0.006
Previous R.A.I.	13.8	0.032
Exophah.	19.6	0.003
Current Cbz.	12.9	0.044

Effect of removing a discriminant function on the resdiual discriminating power

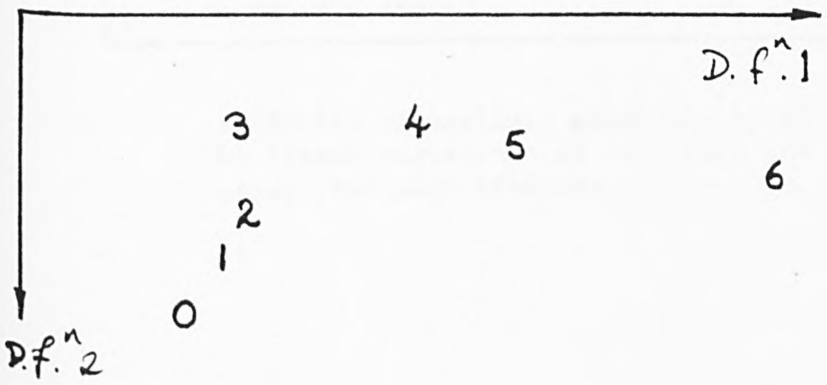
Removing d.f.^{n}	Significance
0	0.000
1	0.002
2	0.608

Other functions thus have negligible effect.

Overall classification rate on this data - 64%

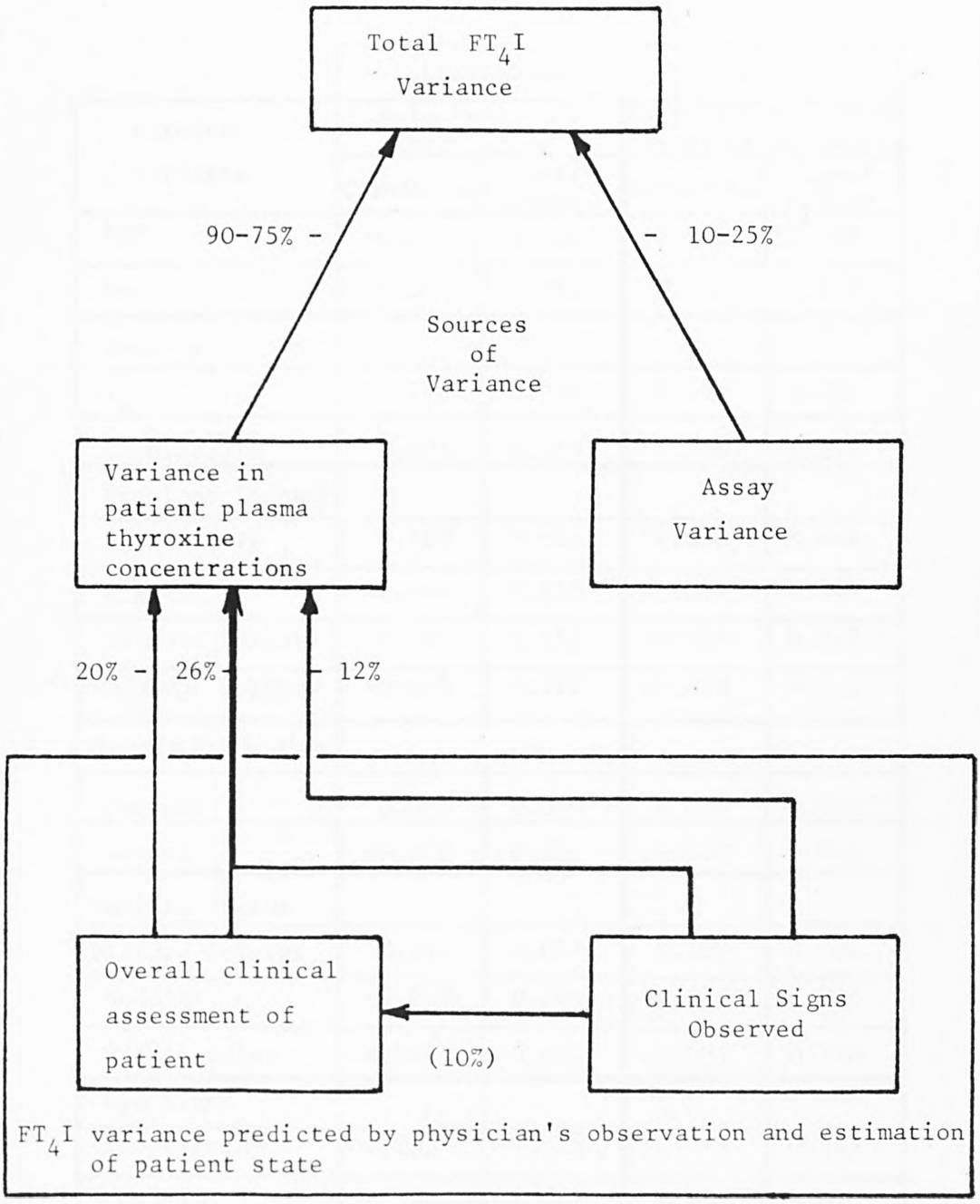
		Predicted class						
		0	1	2	3	4	5	6
Actual Class	0	0	0	1	6	0	0	0
	1	0	0	2	14	0	1	0
	2	0	4	6	115	1	0	2
	3	0	0	9	411	8	0	3
	4	0	0	0	38	6	0	5
	5	0	0	0	18	3	0	4
	6	0	0	0	5	2	0	5

Pattern formed by classcentroids in space of 1st two Discrm. f^{ns}.



Class	Assessment
0	Def. Hypo.
1	Prob. Hypo.
2	Poss. Hypo.
3	Prob. Euthy.
4	Poss. Hyper.
5	Prob. Hyper.
6	Defn. Hyper.

Figure 5.25



Estimates of variance predicted by clinical data obtained by linear regression on J.N. Data and examination of assay precision profiles

Figure 5.26

Effects of Controlling Correlations Between Clinical Signs And FT_4I Results by the Clinical Assessment

Clinical Variable	CORRELATION WITH FT_4I RESULTS			
	Simple Pearson's Correlation		Correlation Controll for Clinical Assess	
	Correlation	Signif-icance	Correlation	Signif-icance
Age	-0.015	0.386	0.044	0.198
Sex	-0.052	0.091	0.108	0.018
Therapy				
T_4	0.118	0.001	0.171	0.001
Carbimazole	0.074	0.028	0.036	0.245
Previous Therapy				
Carbimazole	0.153	0.001	0.088	0.044
R.A.I.	-0.045	0.125	-0.007	0.448
Thyroid Surgery	-0.042	0.141	-0.054	0.145
Pituitary Surgery	-0.019	0.311	-0.054	0.145
Thyroid Antibodies				
Present	0.066	0.045	0.064	0.050
Absent	-0.029	0.224	-0.032	0.202
Goitre Status				
Diffuse Enlarge	0.210	0.001	0.102	0.004
Nodular	-0.049	0.104	-0.050	0.098
Multinodular	-0.066	0.044	-0.037	0.170
Eye Signs				
Exophthalamos	0.083	0.016	0.012	0.381
Lid-lag	0.155	0.001	0.081	0.019
Other signs	-0.039	0.155	-0.011	0.386
Pituitary Disorder	-0.030	0.222	0.010	0.394

Figure 5.27

Linear Regression of Clinical Assessment Upon Subsequent FT_4I Assay Results

Clinical Assessment		R^2 Change	Significance
Hyperthyroid	Definite	0.063	0.000
	Probable	0.061	0.000
	Possible	0.005	0.226
Hypothyroid	Possible	0.041	0.000
	Probable	0.022	0.000
	Definite	0.022	0.000

With all assessments included

Multiple R = 0.45

R^2 = 0.20

Adjusted R^2 = 0.19

Figure 5.28

Relative Frequencies of FT_4I Results by Clinical Assessments for both J.N. Study and K.E.B. Study

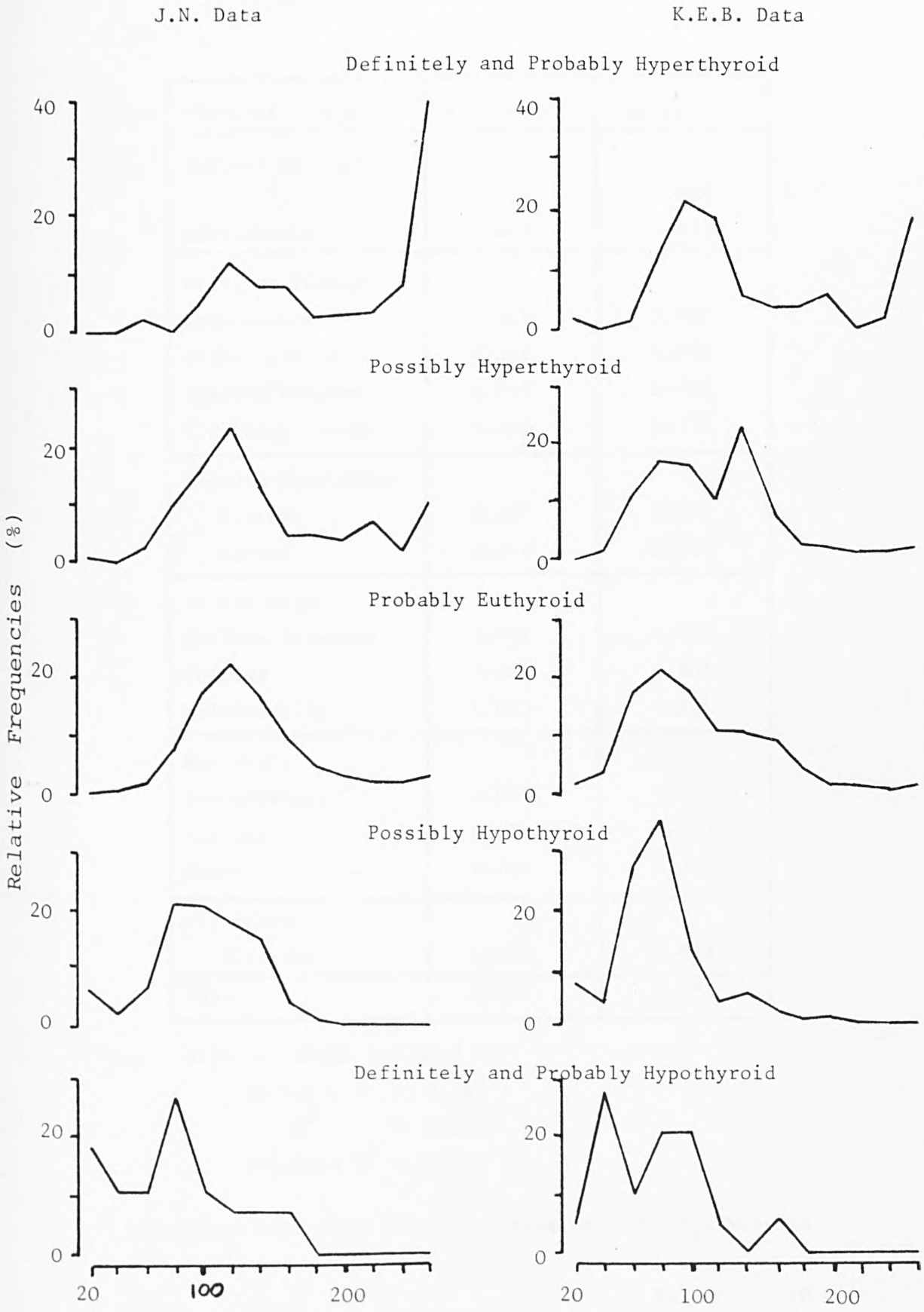


Figure 5.29

Linear Regression of Clinical Signs Upon Subsequent FT_4I Assay Results

Clinical Sign	R^2 Change	Significance	
Current therapy			
T_4	0.014	0.000	*
Carbimazole	0.003	0.634	
Previous Therapy			
Carbimazole	0.011	0.004	*
Radio. Iodine	0.009	0.236	
Thyroid Surgery	0.005	0.288	
Pituitary Surgery	0.000	0.774	
Thyroid Antibodies			
Present	0.000	0.197	
Absent	0.001	0.233	
Goitre Signs			
Diffuse Enlarged	0.031	0.000	*
Nodular	0.001	0.855	
Multinodular	0.003	0.221	
Eye Signs			
Exophthalmos	0.008	0.128	
Lid Lag	0.031	0.000	*
Other	0.001	0.323	
Pituitary			
Disorder	0.000	0.683	
Male	0.002	0.481	

With all signs included

Multiple R = 0.347

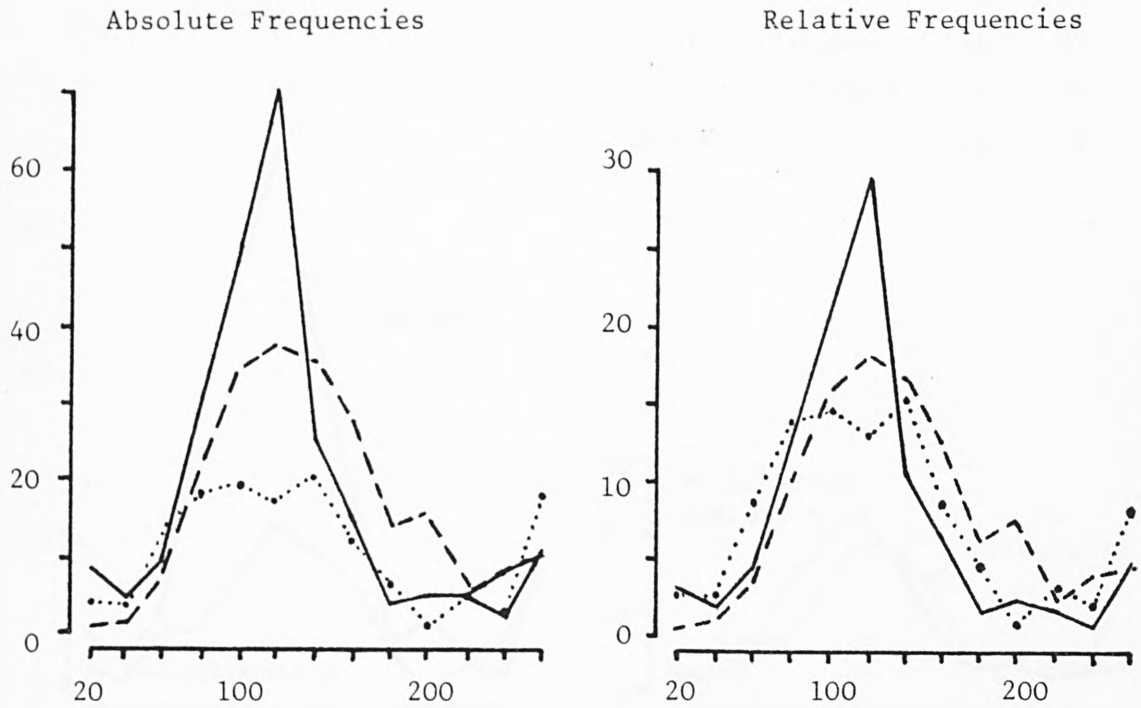
R^2 = 0.120

Adjusted R^2 = 0.098

* Four signs with significant correlation with FT_4I results

Figure 5.30

Distribution of FT_4I results by current therapies



Key	Therapy	Mean	S.D.	N. of Cases
—— No therapy	None	113	57	242
--- Thyroxine (T_4)	Thyroxine (T_4)	132	54	216
··· Carbimazole	Carbimazole	130	77	135

Figure 5.31

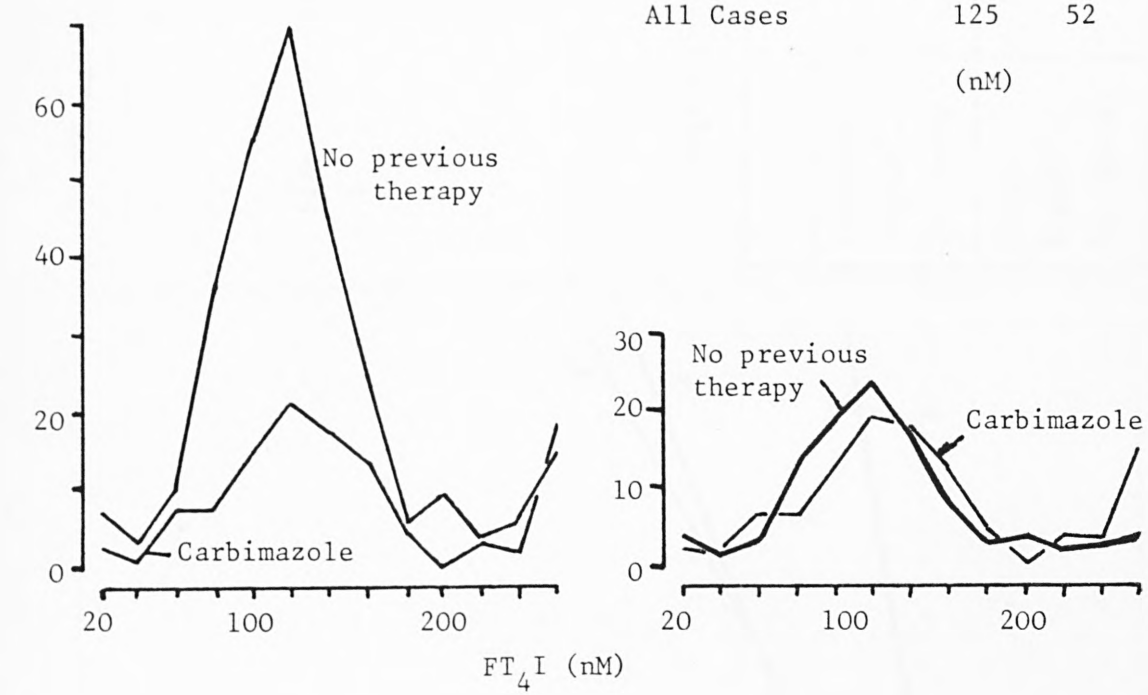
Frequency of FT_4I Results by Previous Therapies

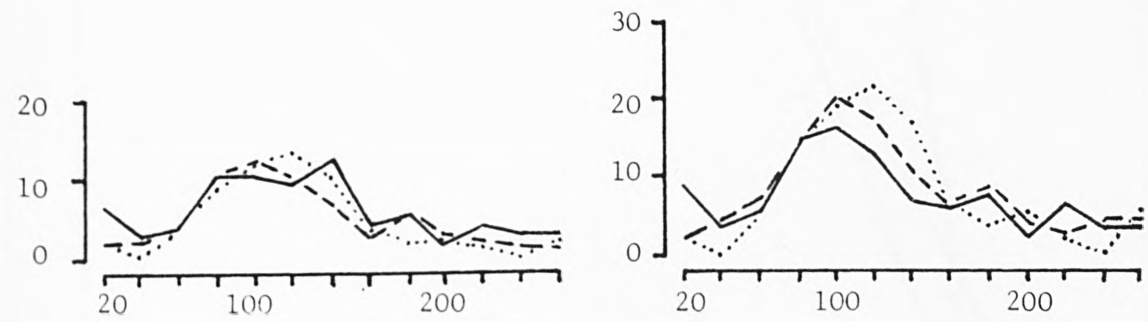
Absolute Frequencies

Relative Frequencies

Previous therapy	Mean	S.D.	N. of cases
None	117	53	290
Carbimazole	142	75	111
Radioactive I.	112	63	71
Thyroid Surgery	114	53	60
Pituitary Surgery	118	56	61
All Cases	125	52	375

(nM)





FT_4I Results in Duo Decades

Lower Figure Key:

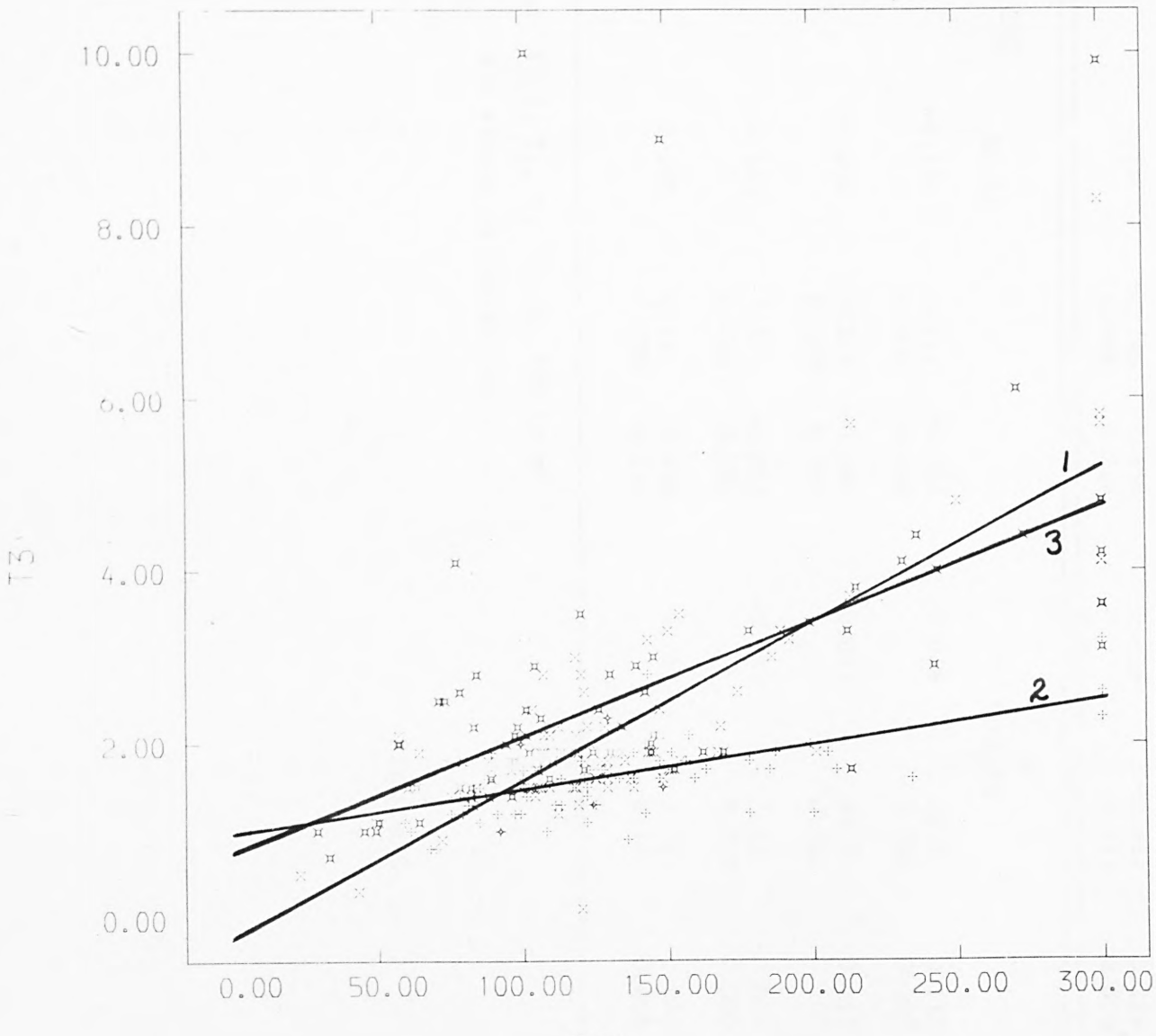
——— Radioiodine

------ Thyroid surgery

..... Pituitary surgery

Figure 5.32

REGRESSIONS OBTAINED ON T_3 AND FT_4I RESULTS ON PATIENTS FROM J.N. DATA SELECTED BY THERAPY



FTI and T_3 in nM

Line	Symbol	Therapy
1	×	NONE
2	+	ON T4
3	¤	CBZ
	◇	PREG

Regression Data

	No therapy	T_4	Carbimaz.
Intercept	- 0.181	0.817	0.801
Signif^n.	0.169	0.000	0.006
St. Error	0.188	0.109	0.312
Slope	0.0179	0.0056	0.0134
Signif^n.	0.000	0.000	0.000
St. Error	0.0013	0.0008	0.0019

Figure 5.33

Dependencies of Assay Results Upon Age and Sex of Patients

Results of linear regression upon data from J.N. study and K.E.B. study

J.N. Study

	MALES			FEMALES		
Assay	Correlation	Intercept	Slope	Correlation	Intercept	Slope
T_4	0.179	94.3 0.000	0.487 0.046	0.000	122. 0.000	0.001 0.497
FT_4I	0.069	103. 0.000	0.213 0.259	-0.151	131. 0.000	-0.169 0.193
T_3	0.285	0.444 0.366	0.038 0.079	-0.123	2.74 0.000	-0.009 0.138
TSH	0.252	-0.748 0.469	0.156 0.214	0.416	-0.621 0.411	0.224 0.000

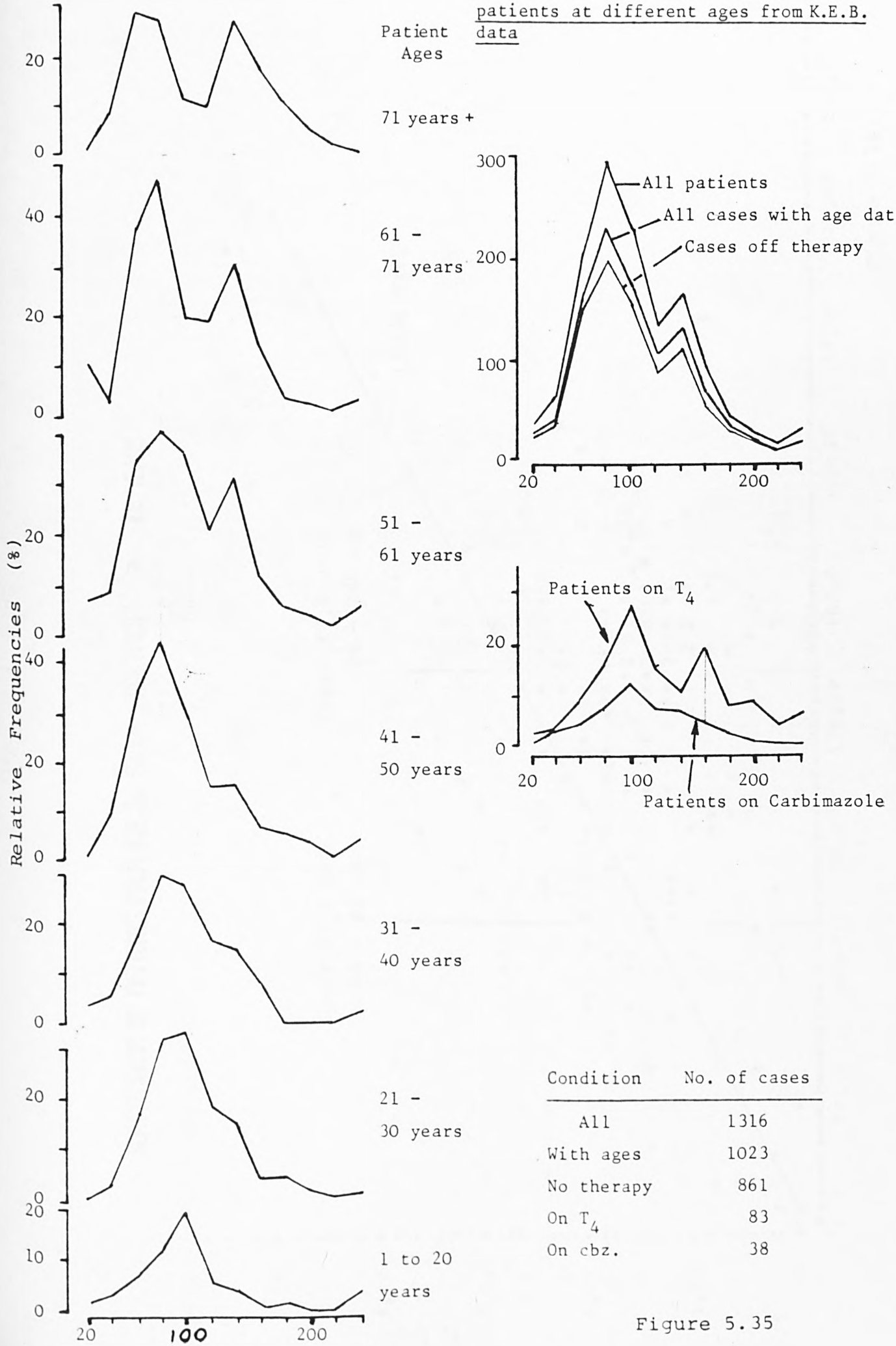
K.E.B. Study

	MALES			FEMALES		
T_4	-0.120	107.7 0.000	-0.263 0.023	0.046	88.2 0.000	0.117 0.102
FT_4I	-0.076	103.5 0.000	-0.190 0.104	0.047	88.2 0.000	0.117 0.102
T_3	-0.343	3.57 0.000	-0.025 0.000	-0.194	3.23 0.000	-0.014 0.000
TSH	0.100	0.71 0.039	0.036 0.110	0.167	2.79 0.14	0.080 0.000

Units: FT_4I, T_4, T_3 in nM, TSH in mU
All slopes in Units/year

Figure 5.34

Variation in FT_4I distribution in patients at different ages from K.E.B. data



Condition	No. of cases
All	1316
With ages	1023
No therapy	861
On T_4	83
On cbz.	38

Figure 5.35

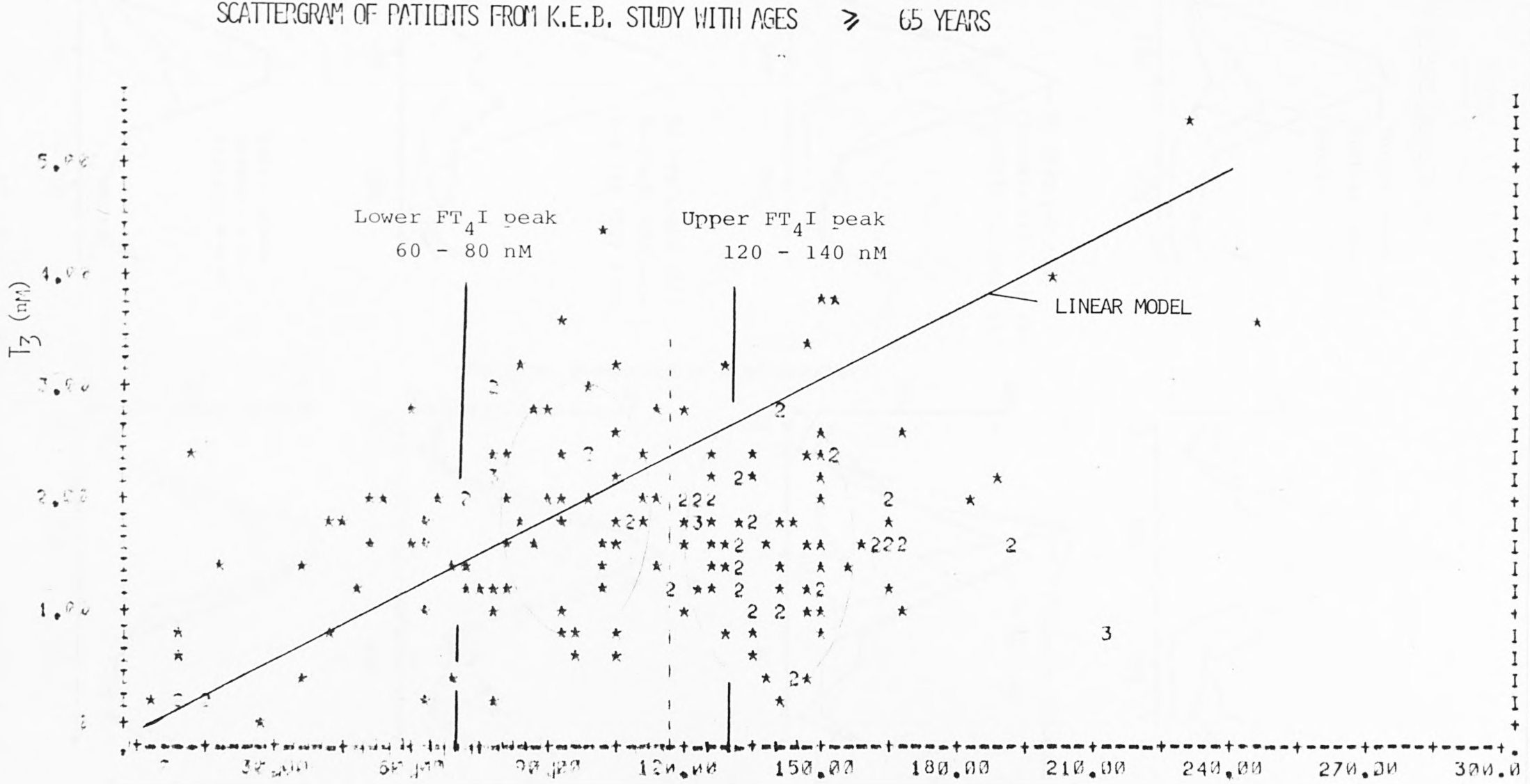
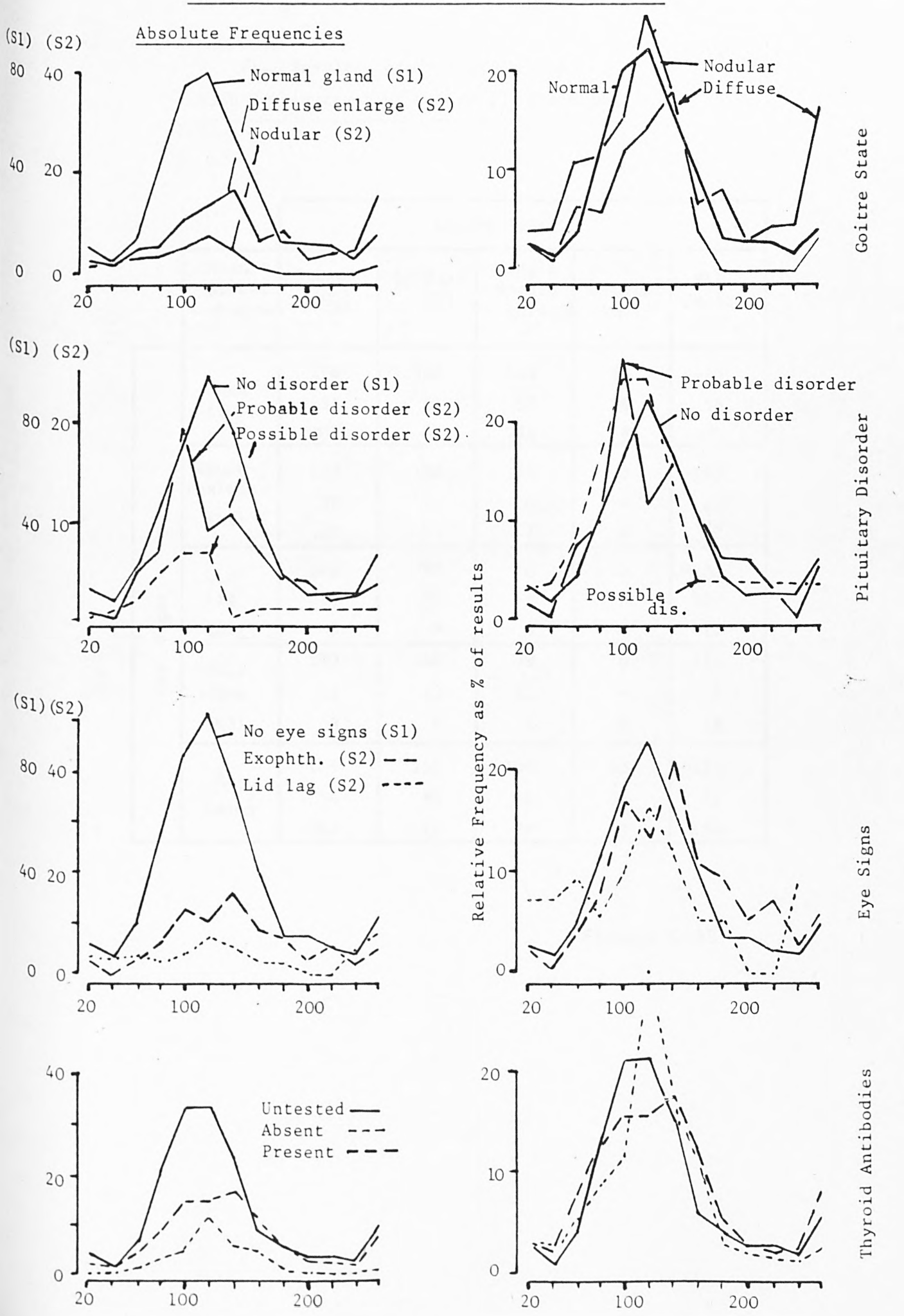

SCATTERGRAM OF PATIENTS FROM K.E.B. STUDY WITH AGES ≥ 65 YEARS
Lower FT_4I peak
60 - 80 nM
Upper FT_4I peak
120 - 140 nM
LINEAR MODEL
T_3 (nM)
FTI (nM)
150.00
180.00
210.00
240.00
270.00
300.0

Figure 5.36

Distribution of FT_4I Results by Clinical Signs



FT_4I Result (nM) in duo decades

Figure 5.37

FT_4I Results Obtained in Patients
With Combinations of Goitre and Eye Signs

Eye Signs	Mean S.Dev. N. of cases	Goitre Signs: None (G0)	Diffuse (G1)	Single Nodule (G2)	Multi-Nodule (G3)	All Cases
	None (E0)	116 51 307	142 84 47	113 67 24	88 36 8	118 58 386
	Exoph-thalmos (E1)	133 55 39	154 72 27	44 - 1	0 - 0	140 63 67
	Lid-lag (E2)	160 115 8	198 102 9	0 - 0	0 - 0	180 107 17
	Other Signs (E3)	100 42 8	146 43 8	79 11 2	0 - 0	118 47 18
	All Cases	118 54 362	151 80 91	108 65 27	88 36 8	123 62 488

Figure 5.38

CHAPTER 6

Dynamic Modelling of Thyroid Hormone Regulation

After the largely "static" analysis of thyroid data in the previous chapters, this and the next chapter will be concerned with an examination of dynamic behaviour observed in thyroid patient data. In the absence of substantial amounts of measurement data as an empirical basis for dynamic modelling, a pre-requisite of any useful clininical application is the introduction of clinical and biochemical knowledge. This chapter is directed towards the development of a more comprehensive model of thyroidal regulation than is currently available. The aim is not a discription of metabolism or even to resolve differing hypotheses, per se but to describe as directly as possible clinically observed behaviour during disease and treatment. It is expected that medical knowledge will direct the selection of structures to be tested but it seems unlikely that any single, tru ly comprehensive, model will be implementated. Instead we are concerned to use the results of this chapter to produce clinically applicable models, an example of which is described in the next chapter.

Paradoxically one of the difficulties is the large body of knowledge which exists on thyroidal metabolism. It is tempting to draw upon as much of this information as possible to attempt to resolve it into a consistant whole through the development of the large comprehensive model mentioned above. Unfortunately the modelling exercise can become self-justifying, extremely time consuming and finally indecisive. To avoid this no attempt has been made in this work to realise such a complete model. Instead areas of specific clinical uncertainty are examined using the simplest model possible. It is accepted that for final validation the components discussed here should be integrated and fully tested but it is argued that this is not yet a useful course. Indeed, even in the long term, simple easily validated models of components of the thyroidal system are likely to be the important vehicles for hypothesis testing.

6.1 Models of Thyroidal Regulation

Much early work on thyroidal modelling was concerned with iodine metabolism and reflected the comtempory measures of iodine and radioactive iodine tracer studies. An example appears in Berman et al (1968) who consider the development and identification of a compartmental model of the iodine cycle in man. It was the development of sensitive direct radioimmunoassays for the thyroid hormones during the 1960's that switched clinical interest from iodine to the description of changes observed in these hormones. Rather like glucose metabolism, thyroid regulation was quickly identified and feedback models appeared before good measures of thyrotrophin or even before T3 had been distinguished as a separate hormone. Danziger and Elmergreen(1956) had already described a non-linear second order thyro-pituitary model and in the 1956 paper introduced a third-order linear form to explain oscillations seen in some mental disorders (periodic catatonia). The three variables were thyroid hormone concentration, thyrotrophin and a "thyrotrophin activated thyroidal enzyme". The last variable represents an intra-thyroidal pool which acts to increase thyroidal hormone output. The consequence is a degree of integral (ie. destabilising) control in thyroidal feedback which was subsequently introduced by Saratchandran et al (1976) to explain observed plasma T3 changes after TRH stimulation. Danziger and Elmergreen, hovever, had no such T3 or T4 measures and were merely concerned to introduce potential instability into their model. The model was then less able to show the non-linear thyroid hormone/thyrotrophin relationships seen in their previous forms which included saturating non-linearities. Their saturation forms have reappeared in the model developed by Wilkin (1977) who was concerned to explain the steep rise of thyrotrophin levels seen in hypothyroidism and the occurrence of 'sub-clinical' hypothyroidism in some patients. The suggestion is that a saturation or hyperbolic type of response to TSH by the thyroid would explain these effects when thyroid output is reduced during disease. Danziger and Elmergreen discuss the effects of parameter changes and in particular point to the possibility of limit cycles. They do not show any examples or parameter values, either theoretical or clinical, though they report performing simulations and estimation of parameters from clinical observations. These would have

been interesting in the light of observations of circadian cycles in thyroid hormones (Lucke et al, 1977). The conceptual value of the two forms proposed is considerable - providing a cohesive description of a range of clinical effects. The clinical input appears to have been slight for the general reason that estimation of model parameters does not seem to hold out a significant benefit. Once the basic ideas are grasped the physician can use observations directly to select the type of treatment and the authors do not really find a clinical role for the model. These objections can be repeated for much of the work in this area and perhaps this is a factor in the shift by DiStefano from such general thyroidal modelling (DiStefano , 1968) to an analysis of hormone binding (DiStefano and Chang ,1971) and to attempt to identify immeasurable parameters of thyroid hormone production, distribution and disposal (DiStefano et al, 1975). In these later papers DiStefano and colleagues have concentrated upon the binding, distribution and disposal of thyroid hormones rather than the whole thyroid system. Their most recent work has concentrated on the reduction of the number of measures required and exploitation of additional prior knowledge to improve model identification. (DiStefano, 1982a ; DiStefano , 1982b).

In DiStefano III and Chang (1971), the hormone binding proteins were modelled in detail and the authors disputed the usual idea of the binding protein role as that of a buffer, reducing the effect of changes in production on the free hormone concentration. Simulation showed that there was a small degree of amplification of free hormone changes. This arises from the proximity of the specific binding protein (TBG) to saturation. The other, less avid, proteins (albumin and pre albumin) are far from saturation and hence free and bound concentrations follow a nearly proportional relation. The ability to summarise that conclusion in two simple sentences does not remove the need to perform the full analysis to confirm theoretically the effect in a mixture of proteins described by non-linear equations.

Prince and Ramsden (1977) have extended the single binding site per protein model of DiStefano to include all known aspects of interaction between T3 and T4 among the multiple binding sites of the three major binding proteins. The important element in this work lies in the free hormone changes in abnormal conditions. Fresco et al (1982) have

recently confirmed the predictons of the Prince and Ramsden model by comparing direct free hormone measures with calculated values based upon measures of bound hormones and their binding proteins. The only exceptions were the results on pregnant patients where the measured concentrations were significantly lower then the calculated values. Although this work seems to confirm the binding model used, some of the effects included by Prince and Ramsden (ie multiple binding sites for each protien with T3 and T4 competion and negative corparativity between the TBPA T4 sites) are complex and seem likely to have only a small influence upon the final free hormone concentration. Therefore given the error (5 - 10%) in measures it should be clear that these secondary factors remain open to conjecture and their clinical significance is likely to be small.

Recently Pardridge (1981) in contradiction to Robbins and Rall (1960) has argued that the in vitro measures of free hormone do not reflect the amount of free hormone available for transport in vivo. This appears to be based upon a misinterpretation of the model of Robbins and Rall. In particular Pardridge suggests that the free hormone (T4) concentration falls in capillaries during a tissue transit because the half-life of T.B.G. bound T4 is several times the tissue transit time. This misses the basis of Robbins and Rall's argument, that the thyroxine dissociation rate, which is the product of dissociation coefficient and bound hormone concentration, is sufficient to maintain the free hormone concentration even during transit of the liver. At the same time Ekins (1981) has also disputed the free hormone hypothesis but this time on the basis of intra-capillary diffusion effects. In this case the main aim is to find a more specific rate for the binding proteins than a short term reservoir to maintain free hormone concentration during transient falls in thyroidal output. As these aspects are of of considerable clinical interest the work of Pardridge and of Ekins have been analysed in some detail in section 6.2.

DiStefano et al (1975) have turned to the more complex task of quantifying thyroid hormone distribution. To acheive this they reduced the hormone binding subsystem to a simple linear dependence and introduced a three compartment model for the T4 and T3 distribution. The model is linear throughout and is designed to describe small

perturbation studies in normal individuals, the compartments corresponding to plasma, liver, and kidney and finally muscle and skin.

Identification was attempted using perturbation data on three individuals but could not be fully achieved without assumptions about the various distributional compartment volumes. Irvine (1974) has extended this further, though only for animal studies using sheep, by introducing a fourth tissue compartment associated with gut and bone.

The time constants of these various compartments suggest that routine clinical observations, rarely more frequent than weekly, would not reveal their dynamics. For clinical use a simpler equilibrium model would be adequate for most circumstances and prove more tractable than the full parameter form. In section 6.3 a reduced form is developed using available clinical data. Many clinical effects of interest are relatively long-term with changes being observed over periods of months. In contrast response to thyroid hormones or more usually during the TRH stimulation test are sometimes of importance and to describe their dynamics the complete model of distribution may be needed.

Saratchandran et al (1976) had included the DiStefano distribution model into a model of short-term thyroidal regulation. By simulation of response data Sarachandran was able to confirm the need for intergral components in both the thyroidal and pituitary responses. While this is a useful examination of short-term dynamics the model does not address itself to longer term changes. The last two sections of this chapter are examinations of the thyroidal (6.4) and pituitary (6.5) components.

6.2 Diffusion Effects in the Transport of Thyroid Hormones

The significance of the free thyroid hormone fraction in blood as a determinant of clinical states, advanced by Robbins and Rall (1967) has been described in chapter 2 and section 6.1. In summary it is suggested that thyroid hormone, largely bound to serum proteins, must dissociate before transport through the capillary wall and before metabolism in tissue can occur. The liver may be an exception to this rule in that the capillary wall appears permeable to bound hormone but again dissociation is a pre-requisite of transport from intra-cellular fluid

into the cells. The basis of Robbins and Rall's hypothesis that the free hormone concentration, as measured in vitro, is a better indicator of thyroid function then the bound hormone, is supported by their estimates of free hormone loss and bound hormone dissociation rates. They showed that even for tissue with a substantial uptake of hormone (ie liver) the dissociation rate from the slowest dissociating plasma (T.B.G.) is sufficient to maintain without loss the intra-capillary free hormone concentration close to the steady-state equilibrium (without loss). They also showed that the total loss of hormone is normaly never large enough to significantly change the bound hormone concentration. Robbins observed patients with genetic abnormalities in which T.B.G. is wholely absent but who show large reductions without apparent clinical effects. The opposite condition, a rise in T.B.G., is a well established feature of pregnancy and again a disturbance of the total hormone levels occurs without an apparent change in clinical state. In each condition thyroid regulation maintains the correct free hormone concentration. In patients lacking T.B.G. the secondary, non specific, binding proteins (albumin and prealbumin) are sufficient to maintain the free hormone concentration.

As DiStefano and Fisher(1976) have shown that, in the case of T4 at least, the bound hormone does not serve as a buffer to smooth transients in hormone secretion, the role of the bound thyroid hormones appears to be to act as a simple reservoir of almost instantly available hormone. Patients lacking T.B.G. may have been under a disadvantage during an earlier phase of human development in conditions which do not now occur. Otherwise a role for the specifically binding proteins are not envisaged by these workers.

Specific binding proteins are found for a number of hormones but appear only in certain species. T.B.G. in particular, occurs in mammals but not in birds. These and other grounds have lead a number of workers to question the free hormone hypothesis. Oppenheimer and Suiks(1969) and Keller et al, (1969) both considered that some tissues might have transport mechanisms which assisted movement of hormone bound to specific proteins. The result is a system which can direct different amounts of hormone to diferent tissues by changing either the bound or free hormone concentrations. No such protein linked transport

mechanisms have been located and the clinical evidence remains doubtful so these ideas do not appear to have been developed.

More recently Pardridge and co-workers, in a series of papers culminating in a review (Pardridge 1981), have reintroduced the notion that the characteristics of hormone / protein binding may be important in the delivery of hormone to tissue. They claim that the intra-capillary free hormone concentration (the "effective free fraction") is different from the measured in vitro free concentration. Their data are drawn from single pass experiments in which the appearance of active tracer hormone is measured in tissue after the passage of a bolus of active material through the tissue being investigated. An immediate criticism of this work is that the loss rates observed will reflect the disequilibrium of the tracer and not the normal (net) movement of hormone into the tissue. The technique will, however, give an estimate of the capillary permeation rate. The exeception to the above criticism is the case where extra-capillary metabolism is so rapid that dissociation and permeation are rate-limiting . To achieve such high loss rates would require a considerable review of the current estimates of thyroid hormone turnover. More importantly, Pardridge and co-workers appear to have misinterpreted the basis of Robbins and Rall's model by claiming that it implies that only the free fraction of the hormone which enters the capillary is available for transport through the capillary wall. We have described earlier that Robbins and Rall argued that it is precisely the availability of the bound hormone which maintains the intra-capillary free hormone concentration close to the in vitro eqilibrium value. In Pardridge(1981) it is maintained that the long half life of T.B.G. bound thyroxine (32 seconds) compared to the liver transit time (5 seconds) means that little or no T.B.G. bound hormone will be available for transport into liver. A consequence is therefore that only free and albumin-bound hormone will enter liver. This ignores the fact that the (high) T.B.G. dissociation rate , which is the product of the protein/hormone dissociation coefficient and the bound hormone concentration, was the factor which allowed Robbins and Rall to show that the free hormone concentration would be maintained even if T.B.G. were the only binding protein. The appendix to Pardridge(1981) gives a derivation of a model to describe free hormone loss and an

"apparent free fraction" which should be used to correct in vitro measures of free hormone concentration.

As the authors have already "shown" that T.B.G. does not dissociate significantly, their analysis is confined to albumin bound hormone. During the analysis it is argued that, as albumin/thyroxine dissociation and association rates are very high, the free and bound hormones are in quasi - equilibrium and as the change in bound hormone is small the rate of change of the bound hormone can be set to zero. This appears to confuse the swift intra-capillary dynamics of binding (quasi-equilibrium) and the long term changes arising from loss through the capillary wall. Though the change in the bound hormone may indeed be small setting it to zero prevents the bound hormone from dissociating and hence from making any contribution to the hormone lost from the capillary. This is in direct contradiction to the authors' aim of estimating the additional contribution from the bound hormone. Indeed their equations which express the change of free hormone both in and outside the capillary show that neither can exceed the original free hormone fraction. The bound hormone fraction is usually greater than the free , for thyroid hormones the ratio is about 300:1 for T3 and 3000:1 for T4, and as a consequence the dynamics of the large bound compartment dominate. It would therefore be a better approximation in these cases to ignore the free hormone dynamics as it can make a relatively small contribution to hormone transported. The "apparent free fraction" is derived by (an invalid) substitution into the overall capillary mass balance equation. In fact the total mass in the system described is not constant as either bound hormone must be "lost" or free protein created to maintain the total hormone mass constant. One consequence of this analysis appears to be a significant underestimate of the capillary permeability in a number of cases by Pardridge (1980). The correct compartmental analysis would allow useful information on capilary permeation to be extracted from these data.

In conclusion then it appears that neither the data nor analysis presented by these workers bring the free hormone hypothesis of Robbins and Rall into doubt. Ekins (1981) has largely accepted the free hormone hypothesis but has proposed that in certain tissue ,characterised by extremely high loss rates , a dependence upon bound hormone

concentration may arise through intra-capillary diffusion effects. Though direct evidence is lacking, Ekins has suggested the placenta as an example for the transport of thyroxine. The liver too is a site where high loss rates may occur and an hepatic dependence upon bound hormone concentration or a discrepancy between the free hormone concentration seen by hepatic tissue and the observed in - vitro concentration would be of clinical significance.

To investigate fully the possibility of a significant diffusion effect in capillary transported thyroxine, a model of considerable complexity is indicated. Though the Reynolds number for a tube of the diameter of a typical capillary would give a laminar flow, the pulsatile flow, the elasticity and curvature of the capillary and the presence of blood cells of diameter equal to the capillary all indicate an extremely complex and probably turbulent flow. If turbulance is sufficient the system can be simplified to the radially well mixed form usually assumed which has negligible diffusion effects. The association and dissociation rates of the plasma proteins , particularly albumin , are much greater (i.e. faster) than the blood flow rates or hormone loss rates and will give rise to a set of 'stiff' non - linear differential equations (see DiStefano et al, 1975). A further problem is that modelling a complex high order sytem may give a particular numerical solution which will be strongly dependent upon the unknown diffusion rates. It is possible to at least gain insight into the likelihood of significant diffusion effects by examination of only the free hormone compartment under a number of simplifying assumptions. The phenomenon of interest - a dependence of hormone loss upon the bound hormone concentration - will arise through the localised depletion of bound hormone near the capillary wall causing rate-limitation as the bound concentration falls. As diffusion rates are inversely related to molecular size, the free hormone can be expected to diffuse much more rapidly than the bound hormone. If the free hormone diffusion is insufficiently fast there will be no depletion region as free hormone can be drawn from the entire bulk of the intra-capillary bound hormone as soon as dissociation occurs. Another way to express this is to say that if the mean free path of the free hormone is of the order of the capillary radius then diffusion effects will be insignificant. The free hormone compartment has therefore been studied in isolation to determine

whether the necessary diffusion gradient can appear even in the absence of a capillary wall depletion region. If the assumption of radial symmetry is made the element of analysis can be reduced from a toroid (figure 6.1) to the element of figure 6.2. Assuming a single binding site for a single plasma protein, mass balance yields the partial differential equation (6.1) to describe the intra-capillary free hormone concentration.

$$\frac{\partial[H]}{\partial t} = -V.\frac{\partial[H]}{\partial x} + D\left[\frac{\partial[H]}{\partial r} + \frac{1}{r}.\frac{\partial[H]}{\partial r}\right] + kd.[HP] - ka.[P].[H] \qquad (6.1)$$

where: [H] - intra-capillary free hormone concentration
[P] - intra-capillary free protein concentration
[HP] - intra-capillary bound hormone concentration
[He] - extra-capillary free hormone concentration
r,x - radial and axial distances respectively
R,L - capillary radius and length respectively
D - diffusion coefficient for free hormone
kd - dissociation coefficient for P and H
ka - association coefficient for P and H
kp - permiation coefficient for H and capillary
Lr - hormone loss rate from capillary

Consider the effects of making the following additional assumptions:

(i) The system is observed at equilibrium

(ii) The bound hormone is not significantly depleted thus [HP] and [P] are approximately constant

A consequence of (ii) is the appearance of a new equilibrium state, some distance from the start of the capillary, where the dissociation rate has increased sufficiently to balance the loss of hormone from the capillary. Under these conditions the rate of change of [H] with distance down the capillary becomes zero and equation (6.1) reduces to the linear differential equation (6.2)

$$D\left[\frac{d[H]}{dr} + \frac{1}{r}.\frac{d[H]}{dr}\right] - ka.[P].[H] + kd.[HP] = 0 \qquad (6.2)$$

and as [P] and [HP] are constant we can introduce:

$Ka = ka.[P]$ and $Kd = kd.[HP]$ to give:

$$D\left[\frac{d[H]}{dr} + \frac{1}{r}\frac{d[H]}{dr}\right] - Ka.[H] = -Kd \qquad (6.3)$$

At the capillary wall the rate of diffusion of free hormone must equal the rate of loss through the wall so the boundary condition is :

$$D.\frac{d[H]}{dr} = kp.([H] - [He]) \quad \text{at } r = R \qquad (6.4)$$

A particular solution of (6.3) is : $[H] = Kd/Ka$
The homogeneous part of (6.3) is a modified Bessel function which has the solution :

$$[H] = A.I_0(m.r) + B.K_0(m.r) \qquad (6.5)$$

where $m = \sqrt{Ka/D}$
and I_0, K_0 are Bessel series of order zero

Now K (m.r) tends to infinity as r tends to zero so if [H] is finite at r = 0 then B must be zero. Combining the particular and general solutions gives :

$$[H] = Kd/Ka + A.I_0(m.r) \qquad (6.6)$$

Introduction of the boundary condition (6.4) and use of the identity:

$$\frac{dI_0(x)}{dx} = I_1(x)$$

allows A to be determined giving a final solution :

$$[H] = \frac{Kd}{Ka} - \frac{Kd}{Ka} - [He].\frac{I_0(m.r)}{\frac{D.m}{kp}I_1(m.R) + I_0(m.R)} \qquad (6.7)$$

If we introduce E (= Kd/Ka) as the <u>in vitro</u> equilibrium free hormone concentration and substitute F for the fixed denominator of (6.7) then the equation may be rewritten as:

$$[H] = E - (E - [He]).\frac{I_0(m.r)}{F} \qquad (6.8)$$

and it is clear that for a given set of conditions the effect of the radial position upon free hormone concentration arises from the I term. At the capillary wall (r = R) and (6.7) can be rewritten :

$$[H] = E - \frac{E - [He]}{1 + \frac{D.m.I_1(m.R)}{kp.I_0(m.R)}} \qquad (6.9)$$

The system can be described by "lumped" effective resistances to the hormone flow arising from the diffusion within the capillary and the permiation through the capillary wall (see figure 6.3). Under a fixed set of conditions the flow rate is a linear function of the difference between the undisturbed in vitro equilibrium concentration (E) and the extra-capillary hormone concentration ([He]).

$$\text{Diffusion resistance} = \frac{I_0(m.R)}{D.m.I_1(m.R)} \qquad (6.10)$$

$$\text{Permeation resistance} = \frac{1}{kp} \qquad (6.11)$$

6.2.1 Estimation of capillary permeability

Tissue permeability is not known (though see references to Pardridge et al) but a minimum estimate can be obtained by calculating the average rate of loss through all capillary wall for a 70kg man by assuming:

Total body loss of T4 approx. 0.069 $\mu g.min^{-1}$

plasma capillary vol. approx. 165 ml

mean capillary radius approx. 8×10^{-4} cm

Gives a mean capillary length of approx. 8.2×10^{7} cm

Assuming the concentration of free hormone to be 2.5×10^{-5} $\mu g.ml^{-1}$ and the loss rate (Lr) to be given by:

$$Lr = 2.\pi.R.L.kp.([H] - [He])$$

yields a minimum value for kp of 6.7×10^{-3} cm.min^{-1} if [He] = 0 .

6.2.2 Calculation of Capillary Free Hormone Concentration

Assuming for T.B.G. :-

$kd = 1.06$ min^{-1} $\qquad ka = 4.09 \times 10^{4}$ ml.μg.min^{-1} $^{-1}$

$[HP] = 0.1$ μg.ml^{-1} $\qquad [P] = 0.1$ μg.ml^{-1}

$R = 8 \times 10^{-4}$ cm $\qquad D = 3 \times 10$ cm.min^{-1}

The diffusion coefficient (D) is taken from Ross (1980) for the diffusion of free T4 in undisturbed water. Turbulance and the greater plasma viscosity will modify this value which is taken as a minimum estimate. The figures assumed give:

$$R\sqrt{\frac{Ka}{D}} = 2.96$$

And $I_0(2.96) = 4.73$

$I_1(2.96) = 3.82$

Assuming zero mean extra-capillary hormone concentration then:

$$[H]_R = \frac{E}{(1 + 1.12.kp)} \qquad (6.13)$$

Equation (6.13) shows that for even the relatively slowly dissociating proteins such as T.B.G. the free hormone concentration will not fall significantly during normal loss rates. An alternative expression for the free hormone conentration directly in terms of the capillary loss rate Lr may be obtained by using the boundary condition :

$$-D.\frac{d[H]}{dr} = Lr \qquad \text{at} \quad r = R \qquad (6.14)$$

To give from 6.6 :

$$[H]_r = E - \frac{Lr.I_0(mr)}{D.I_1(mr)} \qquad (6.15)$$

The expressions for intra-capillary concentration have been implementated in BASIC on an Apple II microcomputer which allows an easy graphical presentation of the results. A listing of the program appears in Appendix II. Free thyroxine concentration was calculated for a number of different loss and diffusion rates for both T.B.G. and Albumin. The results are presented in figures 6.4 - 6.7 as normalised plots of the free thyroxine concentration relative to the in vitro free hormone equilibrium value at different points across the capillary. Clearly for a normal loss rate no significant free hormone gradient appears for either T.B.G. or albumin. Loss rates must be increased by an order of magnitude before gradients appear and if the effective diffusion rates should be raised, because of mixing, by a factor of 10 even a fifty fold (T.B.G.) or 500 fold (albumin) increase in loss rate will have little effect upon free concentration at the capillary wall. It remains possible for diffusion to limit hormone loss only in tissue with a high permeability and an extraordinary requirement for thyroid hormone. The placenta which may pass substantial amounts of thyroxine on to the larger foetal mass is a possibility but existing evidence is insufficient.

The approximate analysis given above has relied upon the swift re-establishment of an intra-capillary quasi - equilibrium a short distance down the capillary. It is posible to check this assumption for the radially well mixed model which has been established as appropiate from the analysis presented above.

The radially well mixed model is shown in figure 6.8 and the free hormone mass balance yields:

$$\frac{d[H]}{dt} = kd.[HP] - ka.[P].[H] - \frac{kp}{r}.([H] - [He]) \qquad (6.16)$$

$$\frac{d[HP]}{dt} = ka.[P].[H] - kd.[HP] \qquad (6.17)$$

where $[P] = [T] - [HP]$

$[T]$ = total protein conc.

If the changes of bound hormone and free protein are small relative to their concentrations, then the system of equations (6.16) and (6.17) can be reduced to the solution of (6.16) assuming [P] and [HP] to be constants. A consequence of this assumption is the appearance of a new equilibrium some distance down the capillary. If the previous analysis is to be supported it is important that this distance should be relatively small. The solution of (6.16) including the above assumptions becomes:

$$[H] = \frac{Kd}{Ka + Kp} + A.e^{-(Ka + Kp).t} \qquad (6.18)$$

where $Kd = kd.[HP]$

$Ka = ka.[P]$

$Kp = kp/r$

[HP] and [P] here should be the initial bound and free protein concentrations at entry to the capillary which are assumed constant. If the initial free hormone concentration is the <u>in vitro</u> equilibrium value (E) this provides a boundary condition at t = 0 of :

$$[H]_0 = \frac{Kd}{Ka}$$

which can be used to solve for A :

$$[H] = \frac{Kd}{Ka + Kp}\left[1 + \frac{Kp}{Ka}.e^{-(Ka + Kp).t}\right] \qquad (6.20)$$

This appears rather intractable but if the in vitro equilibrium value (E) and the new equilibrium with loss (El) are substituted we obtain:

$$[H] = El + (E - El).e^{-(Ka + Kp).t} \qquad (6.21)$$

where $El = \frac{Kd}{Ka + Kp}$

Which shows the simple exponential decay from the original equilibrium (E) to the new steady state (El) with a time constant Tc :

$$Tc = \frac{1}{Ka + Kp}$$

It is important to recall that this new steady state will not appear if the loss rate is sufficient to make the loss of hormone a significant fraction of the total intra-capillary hormone. The loss in a single transit is found by integration of (6.20) over the capillary transit time (T).

$$TL = Kp.El.\left[T + \frac{Kp}{Ka + Ka.Kp}.\left(1 - e^{-(Ka + Kp).T} \right) \right] \qquad (6.22)$$

The most slowly dissociating thyroid hormone binding protein is T.B.G. so if we take the values used earlier :

$$Kd = 0.106\ \mu g.ml^{-1}.\ min^{-1}$$
$$Ka = 4.09 \times 10^{3}\ min^{-1}$$
$$Kp = kp/r = 8.4\ min^{-1}$$

then $E = 2.591 \times 10^{-5}\ \mu g.ml^{-1}$

and $El = 2.586 \times 10^{-5}\ \mu g.ml^{-1}$

Now Ka is very much greater than Kp so the loss will be a nearly linear function of the binding protein concentration untill Kp is approximately equal to Ka (or until the loss rate had increased by 3 orders of magnitude). Under the existing conditions El is very close to E and the true constant is very short (less than 0.001 min) or less than a tenth of a second compared with a tissue transit of seconds

(approximately 5 s for liver). Clearly until the loss rate increases considerably the tissue transit time is not an important factor in determining the rate of loss from the capillary, and a simple proportionality exists between the transit time (or capillary length) and the total hormone loss for any tissue. In contradiction to the predictions of Pardridge (1981) the transit time does not feature as an important parameter of the ability of thyroid hormone to enter tissue and the in vitro measurement of free hormone concentration remains a reliable indicator of tissue uptake. Finally the brevity of the capillary 'edge effect' confirms the relevence of the analysis of hormone diffusion effects given earlier in this section.

The analysis above has been concerned only with single binding-site models of the hormone and protein. The full picture of protein binding has not yet been worked out but it would appear that the additional sites or the interactions between sites are very much secondary effects. Probably the most complete model of binding remains that by Ramsden and Prince and Ramsden (1977). Recently Fresco et al (1982) have confirmed the agreement between the model estimates of FT4 and FT3, based upon measured total hormone and protein concentrations, and direct free hormone measures from a rage of patient types. Interestingly the only significant discrepancy was between the estimates and measures made on pregnant females where the measured values were lower than those calculated. The authors consider this to be of real physiological difference and not a measurement artifact, but give no hypothesis to explain its occurrence. The discrepancy is, however, within 10% and the model predicts the fall in free hormone concentration seen in these patients. It would therefore seem suitable for use as a currently complete model of thyroid hormone binding. A flow diagram for the calculation of the steady state distributions of T4 and T3 is given by Prince and Ramsden (1977) and these estimates are usually assumed to be satisfactory as the time constants of these binding proteins are much shorter than those of the associated tissues. DiStefano (1976) has discussed the problems which arise when including the complete binding dynamics and has proposed a simplified polynomial approximation.

The original binding systems modelled by DiStefano were simpler than those of Prince and Ramsden but unless great precision is required,

the error introduced (less than 10%) is usually less than the variation observed in measurements. Indeed none of the patient groups measured by Fresco showed less than 10% variation in free hormone concentrations while their overall assay precisions were reported as being between 7 and 11%. Clinical requirements would therefore seem to be met by use of the simple polynomial function proposed by DiStefano (1978) where long-term observations are being considered. Indeed DiStefano has employed a simple linear function for small perturbation studies.

6.3 Modelling of Thyroid Hormone Distribution and Disposal

The model of thyroid hormone distribution partially identified by DiStefano (1975) has appeared in figure 2.6. Even with a high measurement rate and tracer test plasma pool it cannot be fully identified and though recently DiStefano (1982a and 1982b) has made progress in reducing the number of measures and improving the estimates of the parameters, identification of this structure remains impracticable in routine clinical use. Indeed Irvine and Simpson Morgan (1974) had already proposed an even more complex model for T4 transport into muscle which included an interstitial fluid compartment based upon their tracer studies in sheep. Their overall model of T4 kinetics in sheep (Irvine (1974), however, does not introduce interstitial fluid but has three tissue compartments corresponding to: liver and kidneys (fast kinetics, 31% of total body T4) gut and bone (medium kinetics 3% of total T4) and finally muscle and skin (slow kinetics, 44% of total T4). Irvine examined the kinetics of T4 disposal in sheep after a chronic T4 loading which nearly trebled the normal T4 concentration and found a near doubling of some of the parameters of the 'fast' compartment. These observations imply that T4 metabolism is non-linear and that a linearised model of the form used by Saratchandran et al (1976) is inappropriate for severely disturbed patients. Until direct tissue determination of thyroid hormone concentrations and flow rates become possible it seems unlikely that a structure more complex than the form proposed by DiStefano and Fisher (1976) will be useful for the prediction of tissue concentations during hormone dynamics. Even with this structure the remaining uncertainty in parameter estimates suggest that individual variations , particularly when unwell, may make this model unreliable as an improved estimator of tissue (ie. clinical)

status given the comparatively low rate at which routine measurements are made. It should be noted that DiStefano's application of the model was to the estimation of otherwise immeasurable thyrodial secretion and disposal rates.

This introduces the overall secretion and disposal rates for thyroidal hormones which are probably of greater immediate clinical relevance then the details of hormone dynamics. It is important but extremely difficult to try to distinguish between the thyroidal binding compartmental and metabolic effects. The observation that an acute decrease in plasma T3 concentration would occur after an injection of T4 (Woeber et al , 1970) can be predicted from knowledge of thyroid hormone binding. The high concentration of T4 tends to displace T3 from the protien binding sites and the free hormone is then swiftly transported and metabolised. (DiStefano ,1978). In the longer term, changes in plasma T4 or T3 concentrations may arise through changes in hormone disposal and conversion or through modified patterns of secretion. While the model of distribution and disposal remains uncertain it is normally possible to distinguish these elements. An exception arises in hypothyroid patients who have no residual thyroid function (perhaps after ablative therapy) and can be studied without the complexity of variation in thyroidal output.

The conversion of T4 to the three or four times more potent T3 is particularly interesting because of clinical effects during T4 replacement therapy in hypothyroid patients and the possibility of some degree of peripheral control of conversion. A summary of the existing evidence appears to indicate a non-random conversion but whether a simple saturation effect or a specific inhibition by T3 or rT3 could occur, remains uncertain. Wenzal et al (1975) showed that plasma T3 is unchanged for 24 hours after ingestion of T4 by three subjects who all exhibited elevated plasma levels after 4 hours. The plasma T3 levels only appeared to rise about 36 hours after ingestion and after the plasma T4 levels had begun to fall. This might be explained by the existing model of distribution if the major site of conversion was the 'slow' (muscle, half-life greater than 10 hours) tissue rather than the fast (hepatic, half-life less than 1 hour) tissue. Saratchandran et al (1976) had chosen to site all conversion in the fast rather than in the

slow pools. This will not effect the short term T3-dependent dynamics investigated but could have consequences for the delayed T3-dependent pituitary response.

In the longer term we have noted in earlier chapters that those patients receiving replacement T4 therapy seemed to show a lower T3/T4 ratio than apparent euthyroid or hyperthyroid patients. In the K.E.B. data, a distinctly bi-modal T4 distribution was observed in elderly patients. It is interesting to find that prior to the 1970's the recommended T4 dose was 300pg/day - largely because it was believed that extra T4 would be needed to compensate for the absence of thyroidal secretion of T3. The kinetic studies showing that T4 and T3 turnover in patients given this dosage was markedly greater than normal (Braverman et al,1973) and trials with lower dosages of T4 showed that a normal clinical status and T4 levels could be achieved with T4 dosages of 170-200ug/day (Stock et al, 1974). None of these workers, however, noted reduced T3/T4 ratio or the anomalously high T4 results we have observed. Later papers reporting experience with the reduced dosages were examined to determine whether similar effects could be observed but no clear pattern could be discerned (see figure 6.9 in which data are taken from Felt et al, 1977 and Schimmel et al, 1977). Cavaleri and Rapport (1977) discussed the possibility of a non-linear T4 to T3 conversion but did not cite evidence of the type we observe. In fact Kahn (1973) and Murchison et al (1976) had also noticed raised T4 levels in some patients but did not comment further. Recently Ingbar (1982) has made a careful study of patients receiving both Synothyroid and Letter thyroxine whose total plasma T3 and T4 levels were measured by three distinct assay techniques and confirmed a lowered T3/T4 ratio in these individuals. Finally a study by Coli et al (1982) has confirmed that both the total and free T4 concentrations are raised in T4 treated patients without suppression of TSH when treatment is adjusted to maintain plasma T3 in the normal range. The state was seen to arise in the first few weeks of therapy.

The T3/T4 ratio obtained by Ingbar suggests that the missing thyroidal component of the plasma T3 is about 40% though there seems to be considerable variation (10 to 50%). Maguire et al (1976) found that some 61% (ranging from 43 to 77%) of T4 was being converted to T3 per

day. After treatment with 150-200 ug of T4 this proportion fell to 44%. These figures for conversion differ considerably from DiStefano's estimate of appromimately 36% conversion of T4 with T3 secretion accounting for only about 16% of plasma T3. Shimizu et al (1976) found a conversion of 33% in normals, 27% in five untreated hypothyroids and 20% in three euthyroid individuals given large dosages of oral T4. If the assumption that gastrointestinal absorbtion is about 45% than the T4 disposal rate had risen to equal the input rate in those cases given oral T4. T4 disposal increased by a factor of 3 to 5 times while T3 disposal rose by 2 to 3 times. Direct estimates of thyroidal secretion rates are extremely difficult to obtain but Westgren et al (1977) made observations of the thyroid hormone concentrations of thyroid arterial and venous blood in euthyroid patients undergoing surgery. Unfortunately direct measures of thyroidal blood flow ratio were not made but indirect comparison with Shimizu et al (1976) suggests a thyroidal contribution to T3 production of 30%.

A similar study, this time with estimates of thyroid blood clearance by Tegl er et al (1976) gave mean secretion rates which actually exceeded the expected euthyroidal T3 and T4 disposal. This may have arisen from the stress of surgery but Teglier et al show two cases with very high secretion rates and another two without T4 secretion (In the latter cases the portal thyroid hormone concentration was slightly lower than the arterial). Despite the extreme variability shown by these data, it is interesting to observe that the lowest estimate of T3 secretion gave a contribution to T3 disposal of 25%. Again the estimate of disposal rate is taken from Shimizu et al (1976). It is unfortunate that neither of these surgical studies reported any attempt to measure hormone disposal.

Mindroiu and Dimitriu (1976) attempted to estimate T4 to T3 conversion rates in several euthyroid women receiving T4 until 24 hours before the study by observation of I131 T4 and I131 T3 kinetics using a simple two compartmental model. However, the results are expressed as the fraction of T4 converted (36%) which, although this is slightly higher than the value given by DiStefano, cannot be rexpressed as the fraction of T3 produced and so cannot be directly compared with results from the papers refered to earlier. More importantly the absence of a

slow tissue pool in Mindroiu and Dimitriu s' model probably gave rise to the tendency they noticed for the parameter estimates to change over the week of repeated studies rather than it resulting from any underlying alteration in thyroid hormone metabolism.

As the liver is assumed to be a major site of conversion of T4 to T3, changes might be expected in patients suffering from liver failure which might indicate some degree of peripheral control. Green et al (1970) had examined changes in thyroid hormone concentration observed in twenty-three patients with chronic liver disease. These gave T4/T3 ratios shown in the region marked on figure 6.9 An increase in the T4/T3 ratio was seen which may be associated with a failing ability to convert T4 by liver tissue, assumed to be associated with declining serum albumin concentration. The two lines shown in figure 6.9 assume that the amount of T4/T3 conversion is directly proportional to the residual liver function. For the first time T3 and T4 secrtetion by the thyroid are assumed to be simple linear functions of TSH. The second line is drawn assuming that the ratio of T3/T4 secretion is doubled by the increased TSH concentration. In both cases the plasma free T4/ T3 ratios predicted rise as the (linear) conversion of T4 to T3 declines. It can be seen that the, probably more reliable, version which includes TSH effect on the relative secretion of T3 and T4 had difficulty in achieving the observed ratios. This might be taken as evidence for a non-linear conversion of T4 but does not address the possibility of concomitant changes in relative (T4,T3) disposal rates. It might be that these effects dominate and are more closely associated with liver function than conversion which may well (see Wenzel et al, 1975) be a largely peripheral reaction.

Kaptein et al (1982) have examined the kinetics of T4 and T3 in actute illnesses which give rise to lowered T4 levels. Unfortunatly though the authors find '3 - exponetials' neccessary to describe their tracer data no compartmental analysis is performed. As D;Stef ano points out in a review (D;Stefano (1982c)) this type of 'model free' analysis can be expected to distort the estimated parameters. The paper does however show that the T4 and T3 kinetics of these patients are significantly different from normal controls. A second observation was the change in free / total ratios for both hormones. The authors

conclude by proposing that both binding and deiodination are impared in these patients.

A more complex picture of thyroid hormone distribution and metabolism is beginning to emerge and the appearance of improved free hormone assays can be expected to augment this process. Nevertheless considerable uncertainty remains and the increasingly clearly perceived structural complexity suggests a need to turn to the analysis of the underlying and hopefully simpler subsystems. Where this is impossible DiStefano (1976) has emphasised that the careful analysis of any model invoked is a necessary prelude to experimentation.

Ingbar et al(1982), while reporting a lowered T3/T4 ratio in patients receiving thyroxine, also examined the steady state thyroxine dose/response relationship for these patients. Indeed inter-patient variations exceeded the change arising from a two fold increase in dosage. A dependence of plasma T4 upon T4 dosage was found but with considerable inter-patient variation. Unfortunatly no comment on the individual patient dose responses was made at all. This is a typical and important observation with implications for the application of patient models. These large inter-patient variations often swamp out the detailed response to therapy and in this case would exceed the error introduced by assuming a simple linear de-iodination. When observed individually, however, it may be obvious that each is part of a consistent type of behaviour albeit a more or less extreme variant. The consequence is that it may be more useful to be able to specify approximately an individual response than describe the behaviour of the ensemble with great precision. In the particular case of the hypothroid patient's response to thyroxine there seems to be a need for complete information on individual patients over time combined with occasional special tracer models which can establish the parameters of a more realistic model of thyroid hormone distribution and disposal. Finally it is interesting to note that the data presented by Ingbar et al(1982) seem to show that the T3 and T4 results tend to cluster into two groups. One group appears to have normal T3 values and rather raised T4 , while the second group has lower T3 values with near normal T4 results. It is unlikely, though possible, that this reflects a physiological "switching" process and is more probably a reflection of uncertainty by

physicians who choose to normalise either the T3 or T4 result by adjustments of therapy. This selection may in turn reflect merely a random preference or perhaps be associated with the clinical state of these patients. This state of uncertainty and clinical "experimentation" is exactly the condition where a cumulative data-base which includes clinical data can usefully accumulate information of clinical consequence.

As it has not proved possible to resolve the nature of T4 to T3 conversion two forms are offered for simulation work. The first uses the simple linear de-iodination of T4 to T3. The second introduces a slightly more complex "saturating" rate limited conversion. The structure described by DiStefano et al, (1975) and used by Saratchandran et al (1976) has been fitted to the new static observations in the pilot study data of chapters 4 and 5. A check of the parameters used by Saratchandran et al shows that the claimed steady-state values for plasma T3 and T4 are incorrect. In fact the actual steady state values are not even real . The distribution and disposal parameters were not completely identified by DiStefano et al and though assumptions of the various pool sizes more exactly define the parameters there remains some degree of uncertainty. This could be further reduced by specifying the steady-state behaviour of the model. The new parameter values are given in the first of the sets of equations which follow, below the model formulation. This form is required when short-term effects are considered to be of importance - such as the response to a T3 replacement dosage. Amongst the changes made parameter a9 - which specifies the slow pool T4 to T3 conversion - was increased from zero to allow a longer term T3 rise after a T4 input. Wherever protein binding is considered an important factor the model and algorithm proposed by Prince and Ramsden (1979) is suggested for inclusion in the model of distribution and disposal. The algorithm gives "equilibrium" values for free and bound hormone but as discussed by DiStefano et al, (1975) binding kinetics are much faster than distributional dynamics and may be ignored except for very short-term responses or extremely high hormone loss rates. When a reduced accuracy is satisfactory then the polynomial functions of DiStefano (1978) are claimed to be within 10% of the true value.

$$X_1 = a_1 . X_1 + a_2 . X_2 + a_3 . X_3 + U_1 \qquad (6.23)$$

$$X_2 = a_4 . X_1 + a_5 . X_2 + a_6 . X_5 \qquad (6.24)$$

$$X_3 = a_7 . X_1 + a_8 . X_3 + a_9 . X_6 \qquad (6.25)$$

$$X_4 = a_{10} . X_4 + a_{11} . X_5 + a_{12} . X_6 + U_2 \qquad (6.26)$$

$$X_5 = a_{13} . X_4 + a_{14} . X_5 \qquad (6.27)$$

$$X_6 = a_{15} . X_4 + a_{16} . X_6 \qquad (6.28)$$

where X_1 = plasma total T3

X_2 = fast pool total T3 — all in units of μMol

X_3 = slow pool total T3

X_4 = plasma total T4

X_5 = fast pool tatal T4

X_6 = slow pool total T4

U_1 = thyroidal T3 secretion per unit plasma vol.

U_2 = thyroidal T4 secretion per unit plasma vol.

U_1 , U_2 in uMol/hour

Typical parameter values in hours^{-1}

$a_1 = -7.94$	$a_2 = 1.735$	$a_3 = 0.319$	$a_4 = 8.93$
$a_5 = -2.17$	$a_6 = 0.0042$	$a_7 = 0.0237$	$a_8 = 0.054$
$a_9 = 0.00035$	$a_{10} = -1.488$	$a_{11} = 0.8446$	$a_{12} = 0.449$
$a_{13} = 1.645$	$a_{14} = -1.04$	$a_{15} = 0.0066$	$a_{16} = -0.058$

These parameters have been derived from those used by Saratchandran by requiring a realistic steady state

behaviour from the model giving:

X_{1ss} = 1.5 nM X_{4ss} = 90 nM

Reduced Model with Linear Conversion

Whilst the full model above is necessary for the simulation of short term dynamics (up to days) a simpler form is adequate for longer term changes. This may be obtained by retaining only the plasma pools in a 'steady state' version.

$$X_1 = U_1 + A_3.X_4 - A_4.X_1 \quad : U_1 = SRT3/V1 \qquad (6.29)$$

$$X_4 = U_2 - (A_1 + A_2).X_4 \quad : U_2 = SRT4/V2 \qquad (6.30)$$

where

A_1 = 0.04	V1 = 33.0 litres
A_2 = 0.075	V2 = 11.6 litres
A_3 = 0.014	SRT3 = 120 nM/day
A_4 = 0.99	SRT4 = 8 nM/day

A_1 to A_4 in units of day^{-1}

If there is a simple proportionality between the T4 and T3 sectretion rates, that is :

$$\frac{SRT3}{SRT4} = \text{constant} = K$$

then :

$$X_{1ss} = \left[\frac{K.(A_1 + A_2)}{A_4} + A_3 \right] . X_{4ss} \qquad (6.31)$$

Rate limited conversion

The failure of the thyroid gland in hypothyroidism allows the processes of hormone distribution and conversion to be observed independently of regulatory effects. As has been discussed above a non-linear conversion of T4 to T3 has been proposed by various authors

but remains uncertain. The modifications required to the DiStefano model to include rate limiting conversion are shown below. Equations 6.24 and 6.27 must be modified to become :

$$X_2 = a_4 . X_1 + a_5 . X_2 + \frac{a_{61} . X_5}{(a_{62} + X_5)} \qquad (6.32)$$

$$X_5 = a_{13} . X_4 + a_{141} . X_5 + \frac{a_{142} . X_5}{(a_{143} + X_5)} \qquad (6.33)$$

where $a_{61} = 0.00792$ nM/hr | $a_{141} = -1.036$ hr

$a_{62} = 126$ nM | $a_{142} = -0.00792$ nM/hr

$a_{143} = 126$ nM

In a similar way the reduced model can be modified by changing (6.29) and (6.30) to become :

$$X_1 = U_1 - A_6 . X_1 + \frac{A_4 . X_4}{(A_5 + X_4)} \qquad (6.34)$$

$$X_4 = U_2 - A_1 . X_4 - \frac{A_2 . X_4}{(A_3 + X_4)} \qquad (6.35)$$

where $A_1 = 0.075\ day^{-1}$ | $A_4 = 2.38$ nM/day

$A_2 = 6.8$ nM/day | $A_5 = 80$ nM

$A_3 = 80$ nM/day | $A_6 = 0.99\ day^{-1}$

6.4 Thyroidal Secretion

Saratchandran et al (1976) found a simple linear model of the thyroidal secretion rate as a function of plasma TSH concentration inadequate and introduced an integral dependence upon the "history" of the plasma TSH. A logical extension of this model is to associate this

integral effect with protein synthesis and attempt to develop a more general model which would appear to be more closely related to the physical system. Unfortunately these short-term dynamics are of comparatively little interest to the clinical behaviour. In hypothyroid patients who have been treated by T4 replacement therapy the delay observed after cessation of therapy, before the pituitary responds, allows the thyroidal responses to slowly changing TSH levels to be observed. These and other data also indicate that the simple linear model of throidal response should be improved to include the following features:

(i) Thyroidal response to anti-thyroid drugs shows saturation and seems to show a delay in some patients (Rogowski et al, 1977; Mortimer et al, 1977)

(ii) T4 and T3 outputs show saturation in hyperthyroid patients as TSH concentration increases see figure 6.10 derived from Krugman et al(1975).

(iii) Under TSH or thyroid stimulating antibodies (TSAb) the T3/T4 ratio increases intra-thyroidally and in plasma - see figure 6.11 (Krugman et al, 1975; Schimmel et al,1977; Degroot et al, 1977).

In our own data only a few cases were available with sufficient measures to indicate any change in their T3/T4 ratios (figure 6.13), and as may be seen in the earlier chapters a simple linear regression seemed to give a satisfactory fit to euthyroid and hyperthyroid results. It is appealing to combine the rate-limiting model of de-iodination and a thyroidal output which favours T3 output in stress to give the normal T3, low T4 results often seen in hypothyroid patients. In the latter group the increased thyroid output may be largely T3 (T3-toxicosis) and the increased T4 might partly arise from relatively reduced conversion. Figure (6.12) gives a plausible structure which, if combined with a rate-limiting form for synthesis and secretion, would have sufficient degrees of freedom to replicate the observed behaviour. Unfortunately without improved knowledge of the underlying hormone distribution and disposal it would not be possible to estimate the large number of

parameters involved. Instead it is proposed that for clinical purposes a simple linear form be augmented by an intra-thyroidal storage compartment with synthesis dependent upon the presence of anti-thyroid drugs and TSH. The anti-thyroidal drugs appear to block both TSAb and TSH so the two stimuli do not compete. As there is no detailed quantitative information on drug uptake, metabolism and action, an exponential dependence upon dosage is a useful approximation to the more realistic rate-limiting form when simulation and curve-fitting are required.

6.5 Modelling of the Pituitary and Hypothalamus

The use by physicians of the TRH stimulation test of pituitary function to augment the measures of based TSH means that, unlike the thyroid itself, there is a requirement for models which describe both the short term dynamics of the gland and the longer-term changes in disease and under therapy. In practice the clinical test of the pituitary, by TRH stimulation is upon an effectively isolated gland since the thyroid/pituitary feedback pathway will not respond quickly enough. A simpler model can therefore be used to describe the observed TSH levels. This assumes that following an intravenous injection of TRH, a simple exponential release of TSH will result i.e.

If PTSH(t) = Plasma TSH concentration at time t

A = rate constant of TSH release hr

B = plasma TSH loss rate hr

Q = total TSH released per hour

V = plasma volume in litres

Then $C = Q/V$

$$\frac{dPTSH}{dt} = C.e^{-A.t} + B.PTSH(t) \qquad (6.36)$$

Okuno et al (1977) have fitted a similar model to data on children suspected of having one of a number of thyroid conditions. Figure 6.13 gives typical responses and figure 6.14 indicates that some disorders can be isolated by consideration of the three model parameters: a, b,

and y (quantity released in mU/ml/hr). These three parameters together with the value of the basal TSH at time t=0 completely define the response. The model can also be used to derive the optimum times for measurement to discriminate best between particular responses.

An examination of their values shows that the ability of the paramaters to distinguish between different types of patient is not particularly good. In particular if the initial TSH measure is always available then only in the case of pituitary dwarfism is a useful discrimination made. There are insufficient cases to make a final statement but it would be interesting to know whether the overlap in the parameter estimates arise from measurement noise or from the variability of individuals and hence the inherent weakness of the test.

Okuno et al do not have data on the value of the TRH stimulation test in the discrimination of hyperthyroidism or partial failure of the pituitary or hypothalmic function which form the bulk of clinical studies. In these cases the TRH test can be a very useful addition to basal TSH and thyroid hormone measures. Some authors report a distinct "switching off" of pituitary TRH response as the replacement T4 dosage is increased. The difficulty here arises from the observed delay in TSH response after a period of suppression which may make the dose reponse uncertain.

Saratchandran et al (1976) had used a similar log-linear second order model to describe the data of Snyder et al (1973) to show that the TSH response is a logorithmic function of the TRH concentration. We have confirmed this by fitting a difference equation form of Sarachandran's pituitary model to Snyder's data. Figure 6.15 shows the TSH and log TRH reponse for the five TRH doses when the model of equation 6.36 is fitted simultaneously to all responses. In practice these five parameters cannot be identified directly and an iterative procedure was adopted, using initial estimates of the TRH and TSH half-lives. The results shown in figure 6.15 were obtained after three steps starting from an initial guess of the TRH half-life as used by Saratchandran. There is generally good agreement with the TSH observations. However, the tendency for the model response to be high at extreme and low at the intermediate doses does suggest that the

logarithmic dependence upon TRH is insufficient to describe the saturation of output at high TRH dosage. Two other clinical limitations of the basic Sarachandran model must be noted. The long-term response of the model to falling thyroid hormone levels is not realistic in either the linear or the unconstrained integral terms. Data from Larsen (1978) suggest that an exponential response may be a more realistic approximate description of the TSH/T3 dependences. Secondly, the TSH response to TRH of a hypothyroid patient, though considerably greater in absolute quantity of TSH released than in the case of a euthyroid subect, is distinctly smaller relative to the normal basal output. An examination of the physiology of the pituitary may give an indication of the reason for this. Mitsuma et al (1976) observed a twenty-fold increase in plasma TRH in hypothyroid patients suggesting that the hypothalmus also responds to the lowered thyroid hormone levels to drive the pituitary harder. The pituitary is located close to the hypothalamus and small capillaries pass from the hypothalamus directly into the pituitary. This can be expected to have two effects. Firstly, the TRH concentration arising from endogenous sources seen by the pituitary will be greater than the measured plasma value. The actual difference will be a function of the rates of hypothalmus to pituitary capillary flow and the peripheral metabolism of TRH. This could explain the relatively high doses of exogenous TRH required to obtain a detectable pituitary response. A relatively low capillary flow could give rise to a second effect by limiting the rate at which TSH can be released into the peripheral circulation.

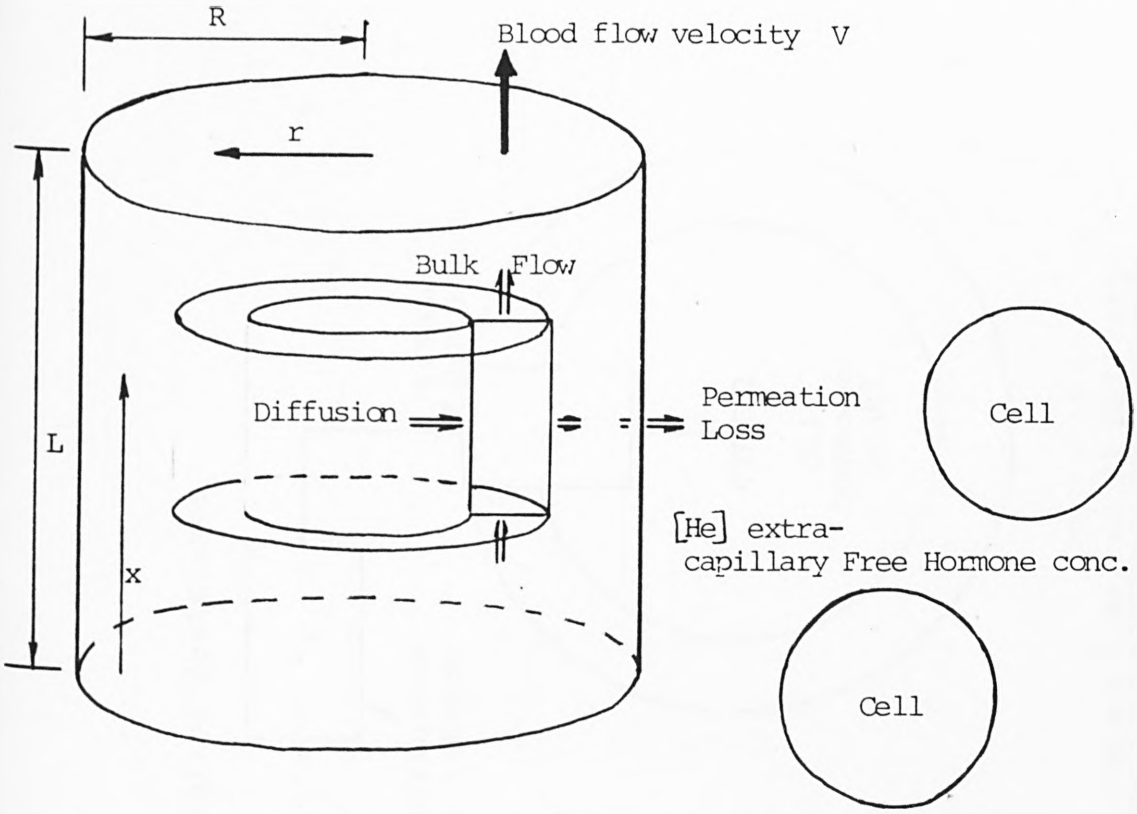
A model with a simpler secretory response to TRH than the logarithmic form used by Saratchanran may be introduced by introducing a pituitary reservoir. This resevoiur may be exhausted by the secretion of TSH during the TRH stimulation test. The degree of emptying could then give rise to the saturation effect seen as the TRH input is increased. Indeed the bi-phasic TSH response to a continued (step) TRH stimulus might then correspond to the initial emptying of an intra-pituitary pool followed by a continuing output either by protein synthesis or through the migration of TSH granules from the thyrotroph's interior. Unfortunately simulation of a simple intra-pituitary pool model shows that as the TRH impulse input increases the time to the plasma TSH peak is reduced. In fact the data of Snyder et al, (1973)

suggest the possibility that the TSH peak occurs earlier as the TRH stimulus is increased but the observed change is small. As noted above introduction of compartments to describe the intra-capillary TRH and TSH concentrations will not reduce this effect unless the capillary flow rate is slow enough to limit the secretion of TSH into plasma either by inhibition of transport across the pituitary membrane or by simple flow limitation.

Attempting to resolve the structure and behaviour of this system in the light of the growing amount of experimental data is an attractive problem but probably not of direct clinical application. The longer term changes in TSH appear to follow a hyperbolic or exponential form (Larsen 1978) when a whole group of patients are considered. Krugman et al (1975) showed delays in the TSH response to falling thyroid hormone levels in patients taken off long-term T4 therapy. An initial clinical model of pituitary response would therefore have to include these features.

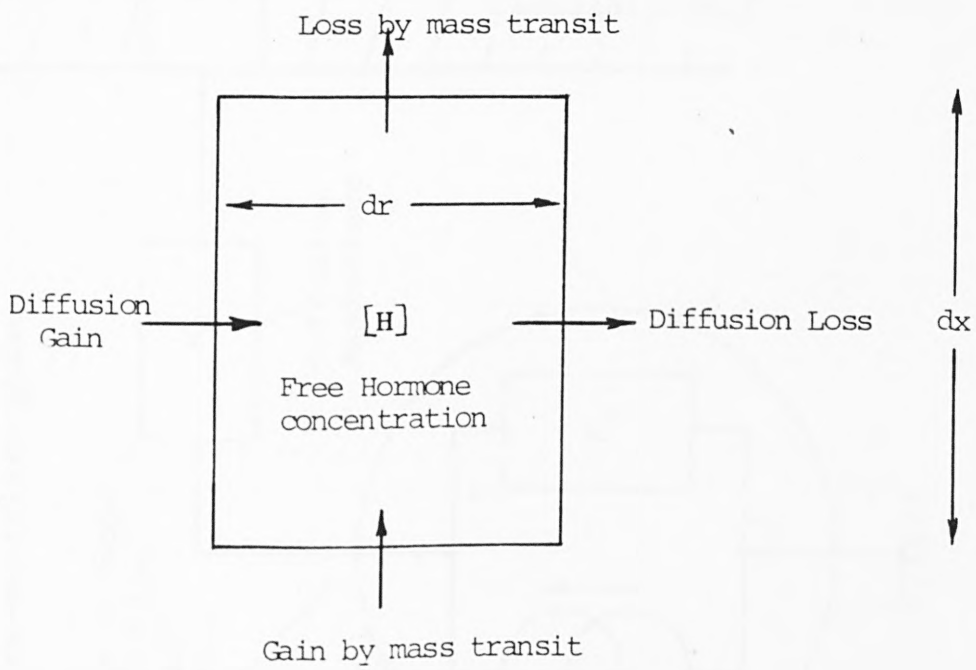
6.6 Conclusions

We have examined some relevent aspects of dynamic models of thyroid function in this chapter to attempt to distinguish the necessary components of a clinical model. Clearly it would be as inappropriate to introduce models of the complexity described here as it was to ignore the dynamics of patient behaviour entirely. The next chapter therefore attempts to produce and test a synthesis of the most clinically important aspects of these models.

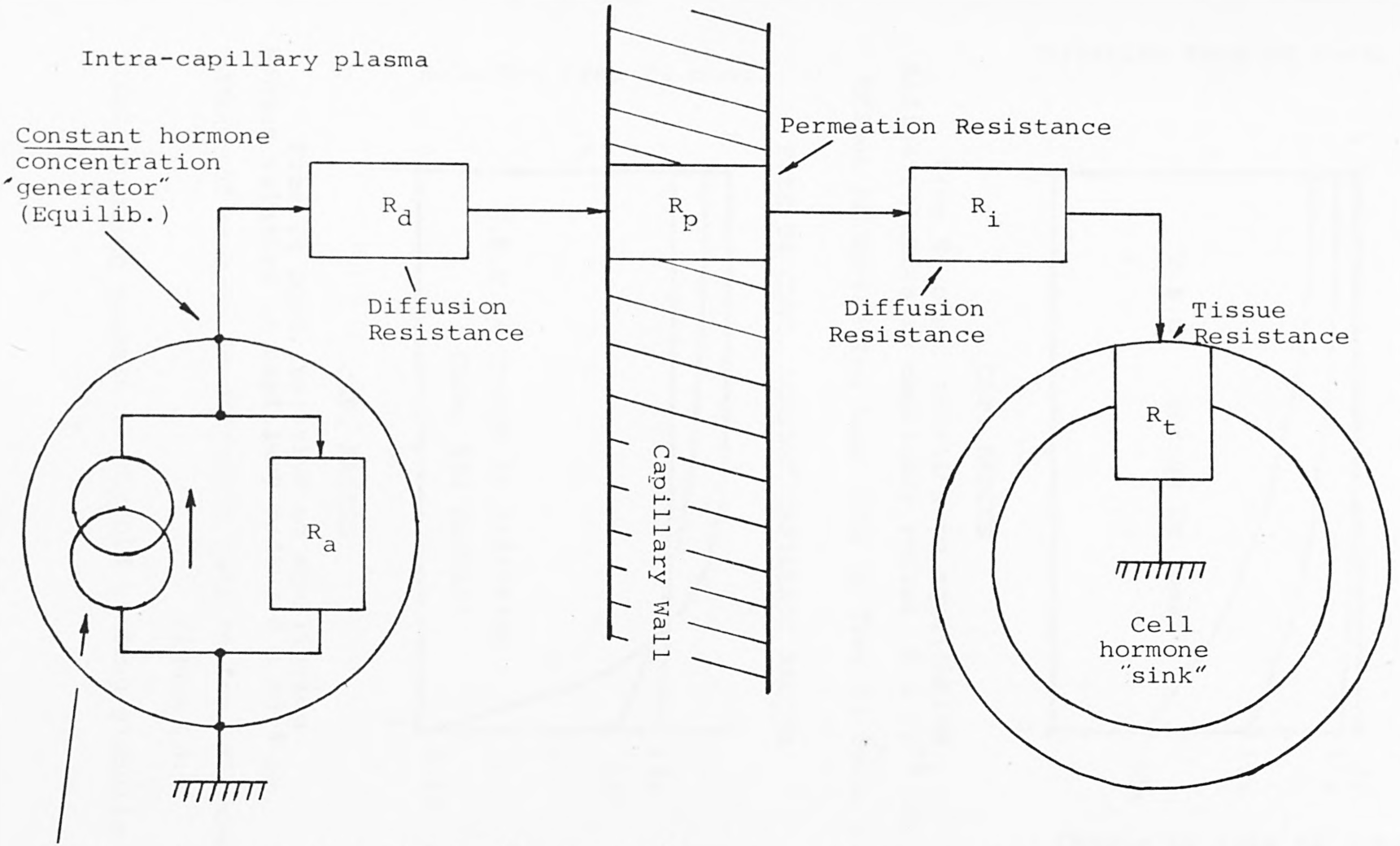


Toroidal region for analysis of intra-capillary free hormone conc.

Figure 6.1

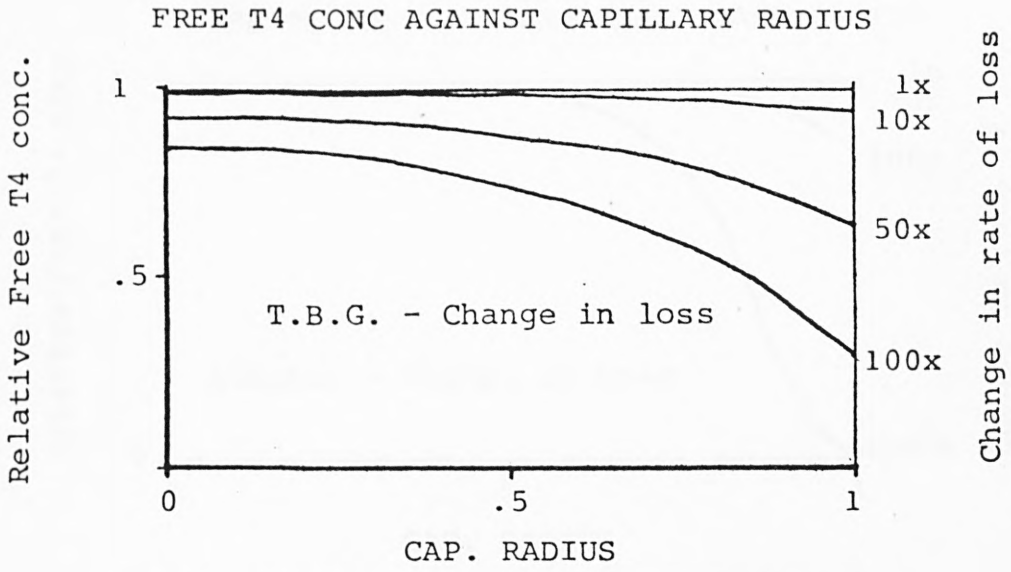


Rectangular element derived by symmetry from toroid Figure 6.2



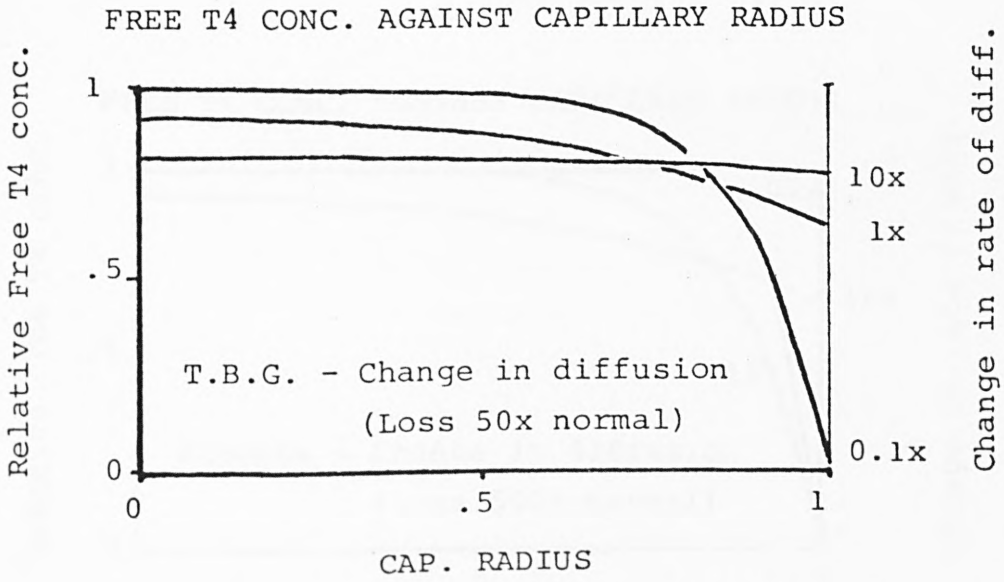
A lumped model of T4 delivery

Figure 6.3



Free T4 conc. relative to equilibrium
Radius relative to capillary radius 8×10^{-4} cm.

Effect of increasing loss rate on free T4 conc. Fig.6.4

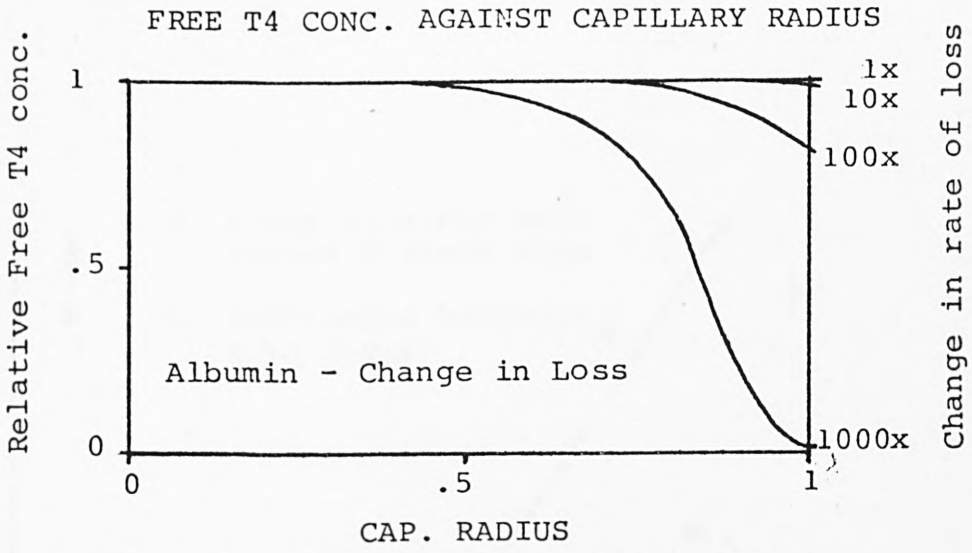


Free T4 conc. relative to equilibrium
Radius relative to capillary radius 8×10^{-4} cm.

Effect of changes in diffusion rate on free T4 conc.

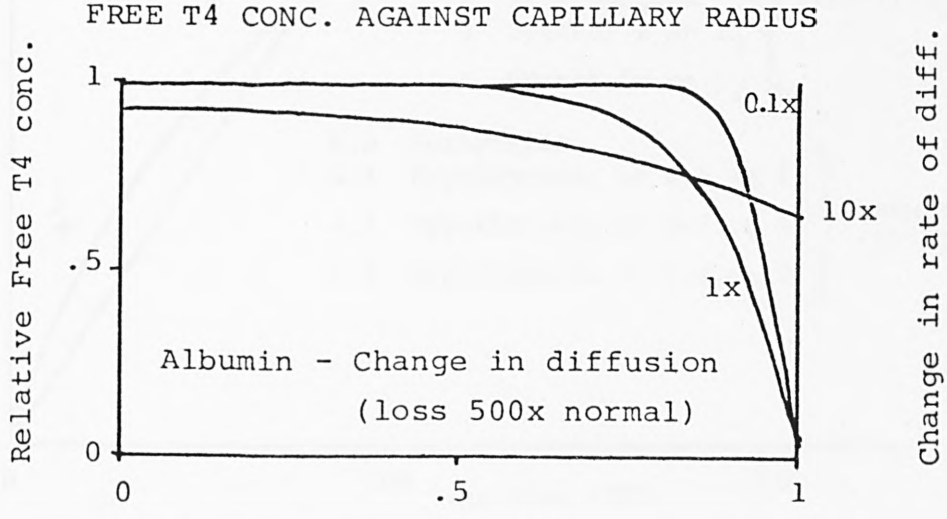
Figure 6.5

Single binding protein :- Thyroid binding globulin



Free T4 conc. relative to equilibrium
Radius relative to capillary radius 8×10^{-4} cm.

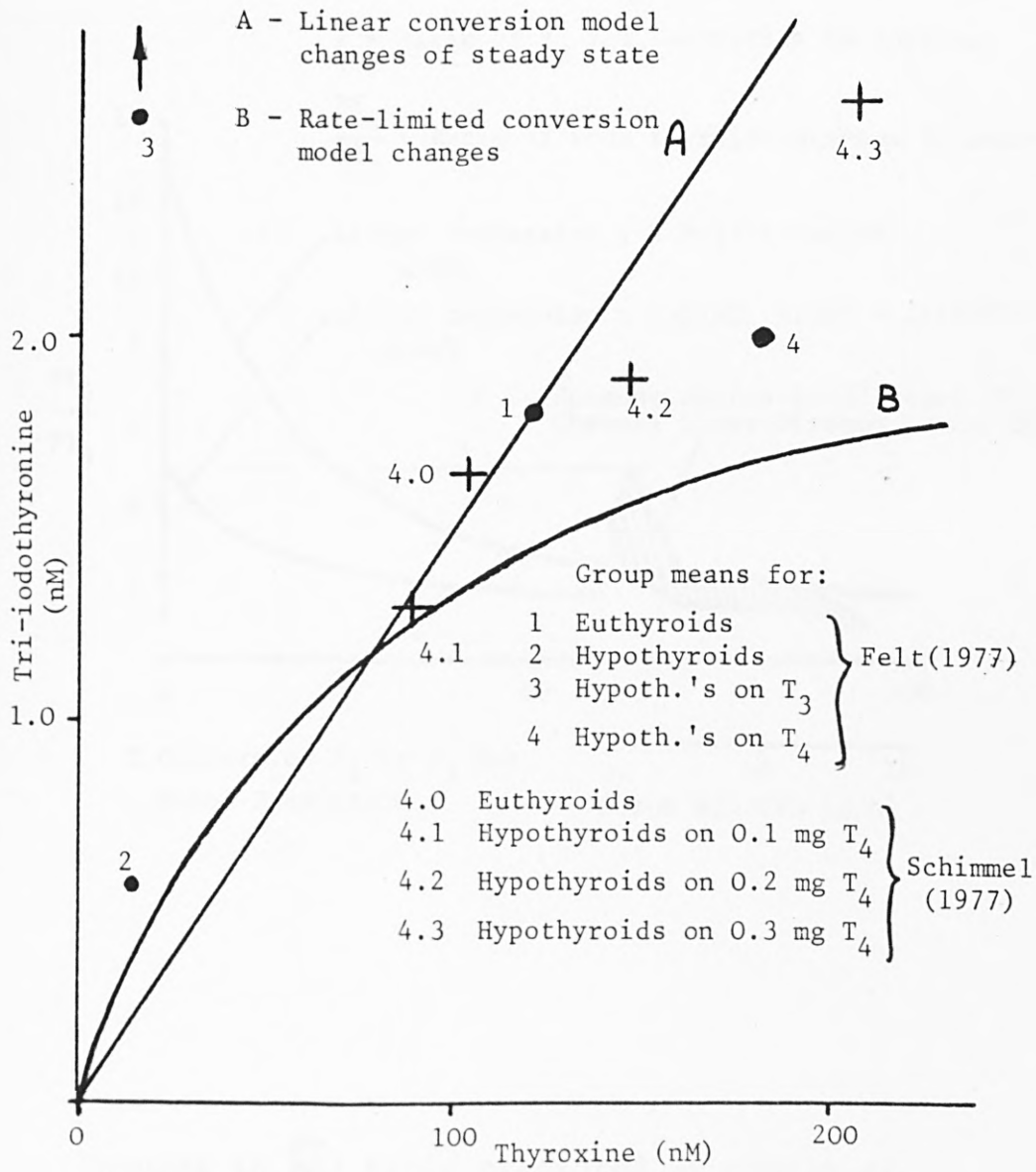
Effect of increasing loss rate on free T4 conc. across capillary for albumin binging only Figure 6.6



Free T4 conc. relative to equilibrium
Radius relative to capillary radius 8×10^{-4} cm.

Effect of increasing diffusion resistance on free T4 intra-capillary concentration, albumin binding only

Figure 6.7

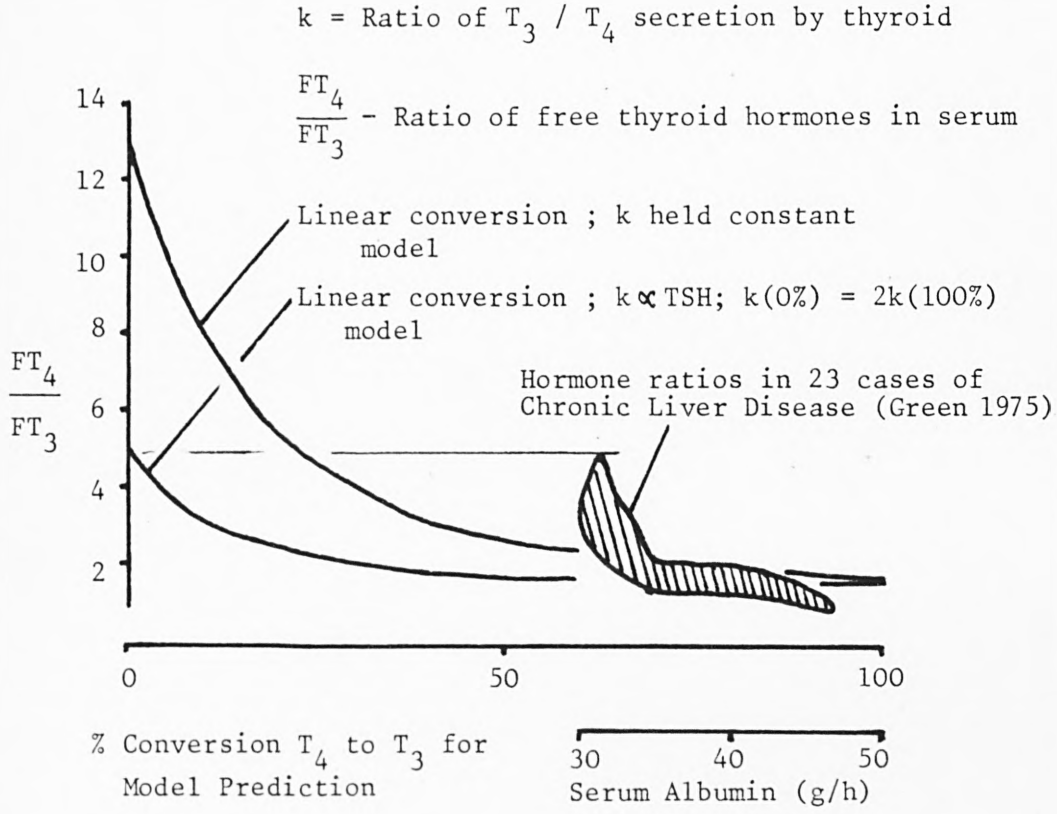


Comparison of steady-state changes in T_3 and T_4 for Linear and Rate-limited conversion of T_4 to T_3

Linear vs. rate limited conversion of T_4 to T_3 points plotted are patient mean values while on T_4 replacement therapy

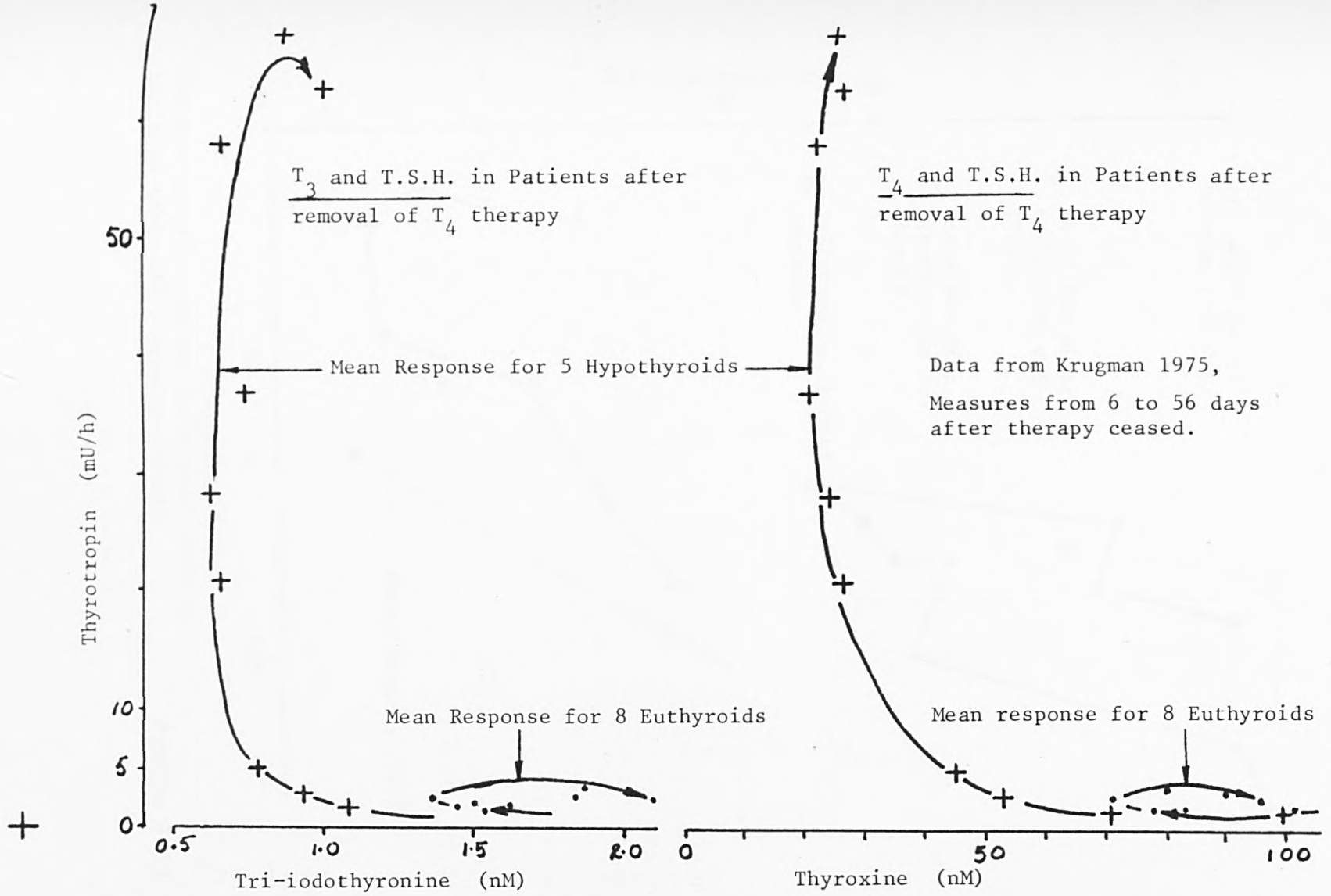
Figure 6.8

Prediction of FT_4 / FT_3 Ratio by Linear Conversion Model

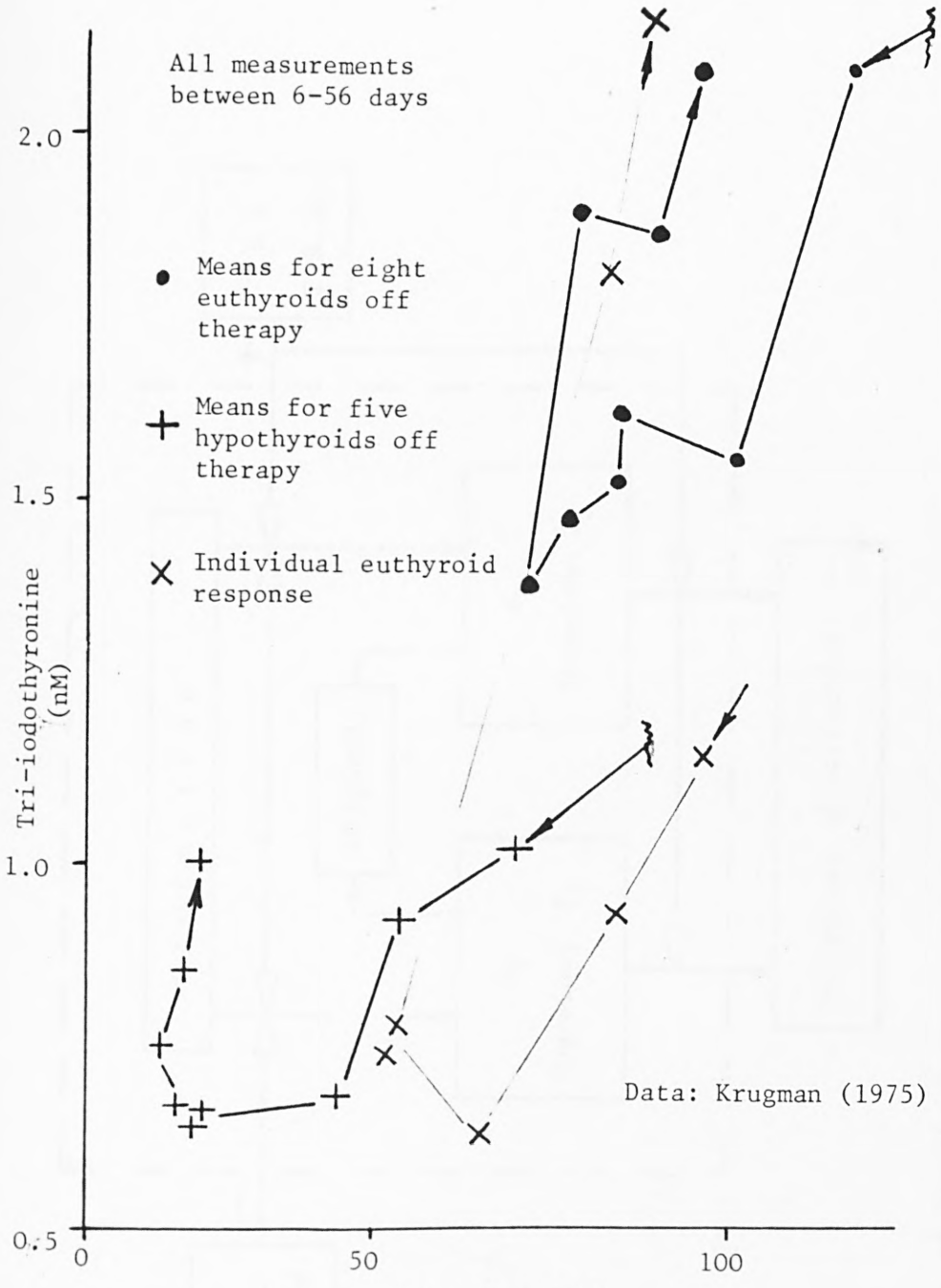


Changes in $\frac{FT}{FT}\frac{3}{4}$ ratio predicted by models vs. observed changes during chronic liver disease

Figure 6.9

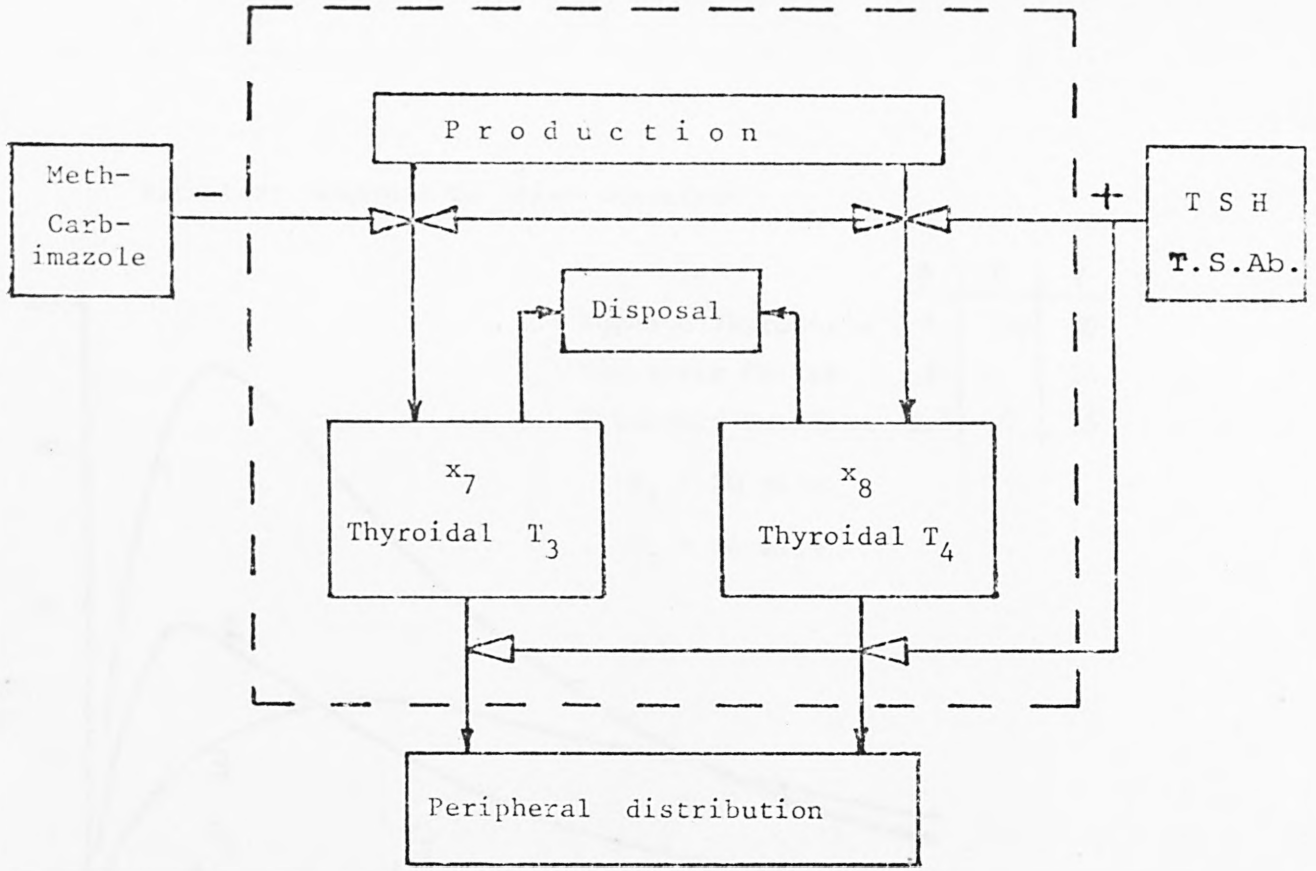


Responses of Hypothyroids and Euthyroids to T.S.H. after T_4 induced suppression Figure 6.10



Changes in thyroxine and tri-iodothyronine in patients taken off thyroxine therapy

Figure 6.11



Model of Thyroid Hormone Production and Secretion

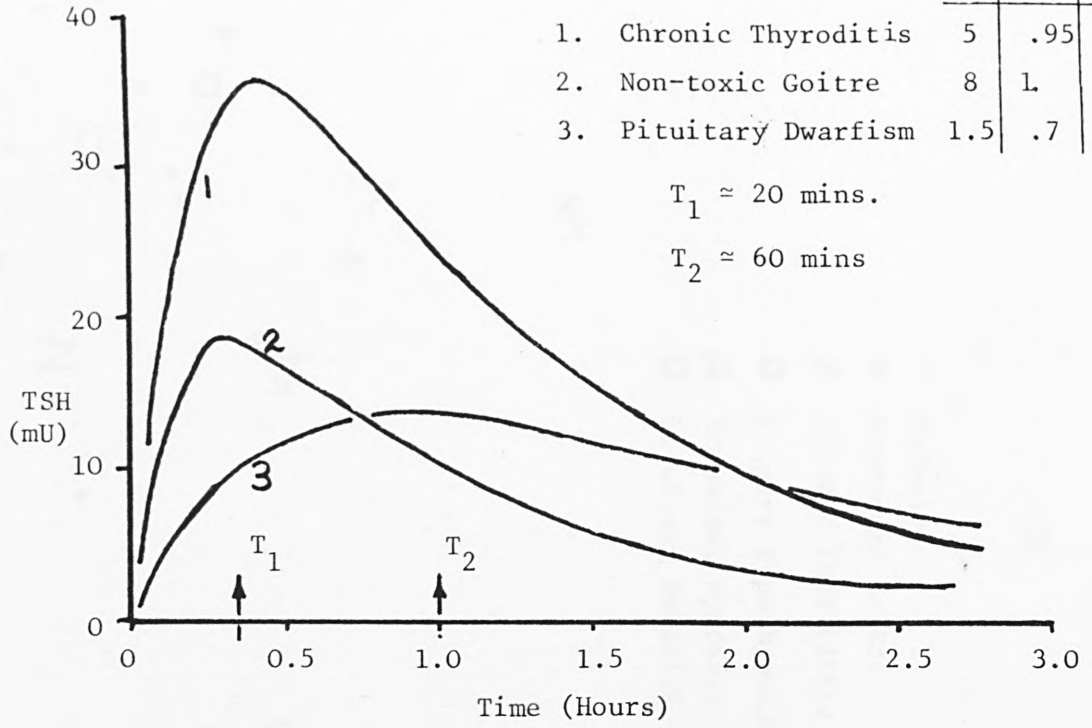
Figure 6.12

Pituitary Response in three disorders

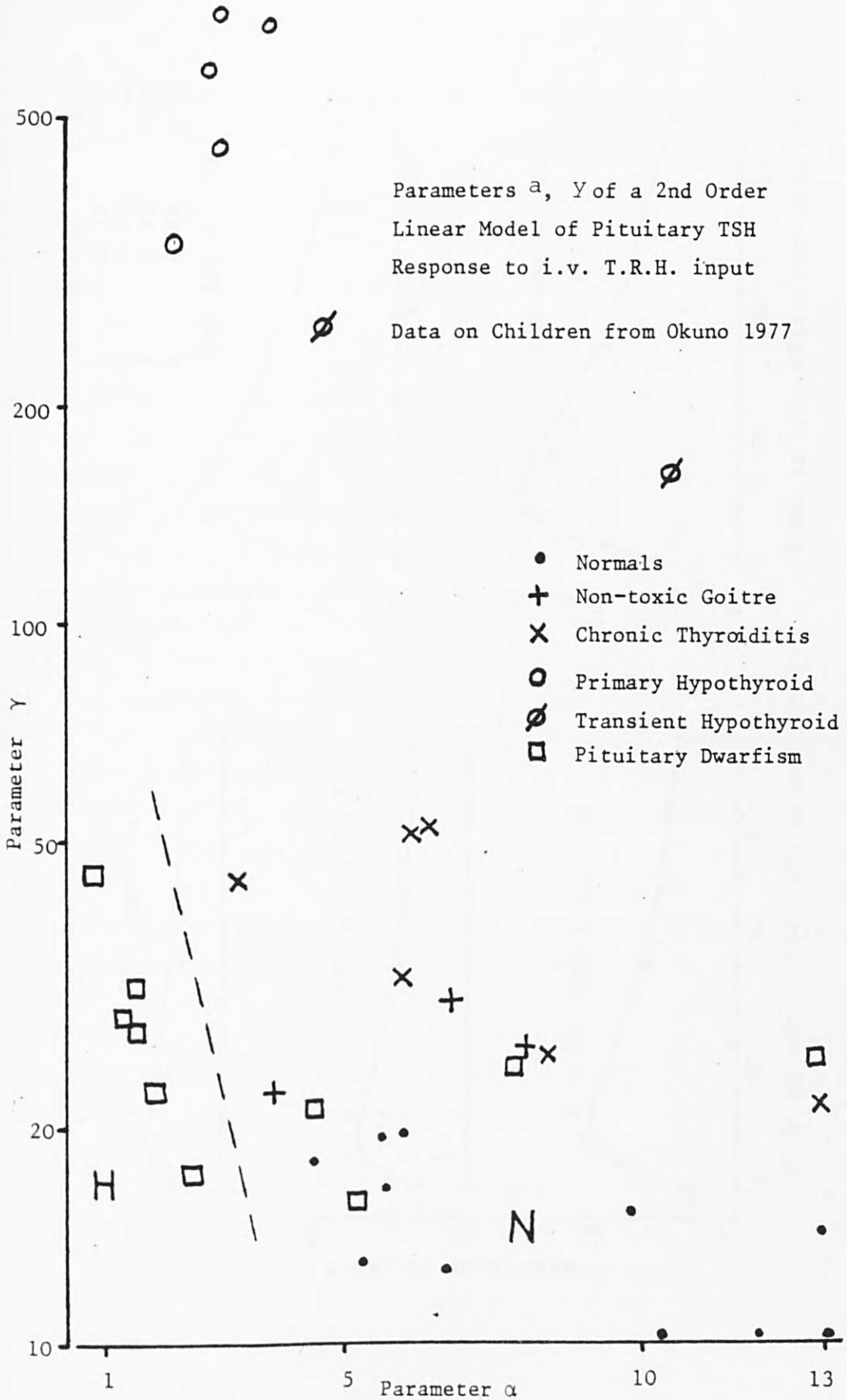
	a	b	y
1. Chronic Thyroditis	5	.95	50
2. Non-toxic Goitre	8	1.	24
3. Pituitary Dwarfism	1.5	.7	25

$T_1 \simeq 20$ mins.

$T_2 \simeq 60$ mins

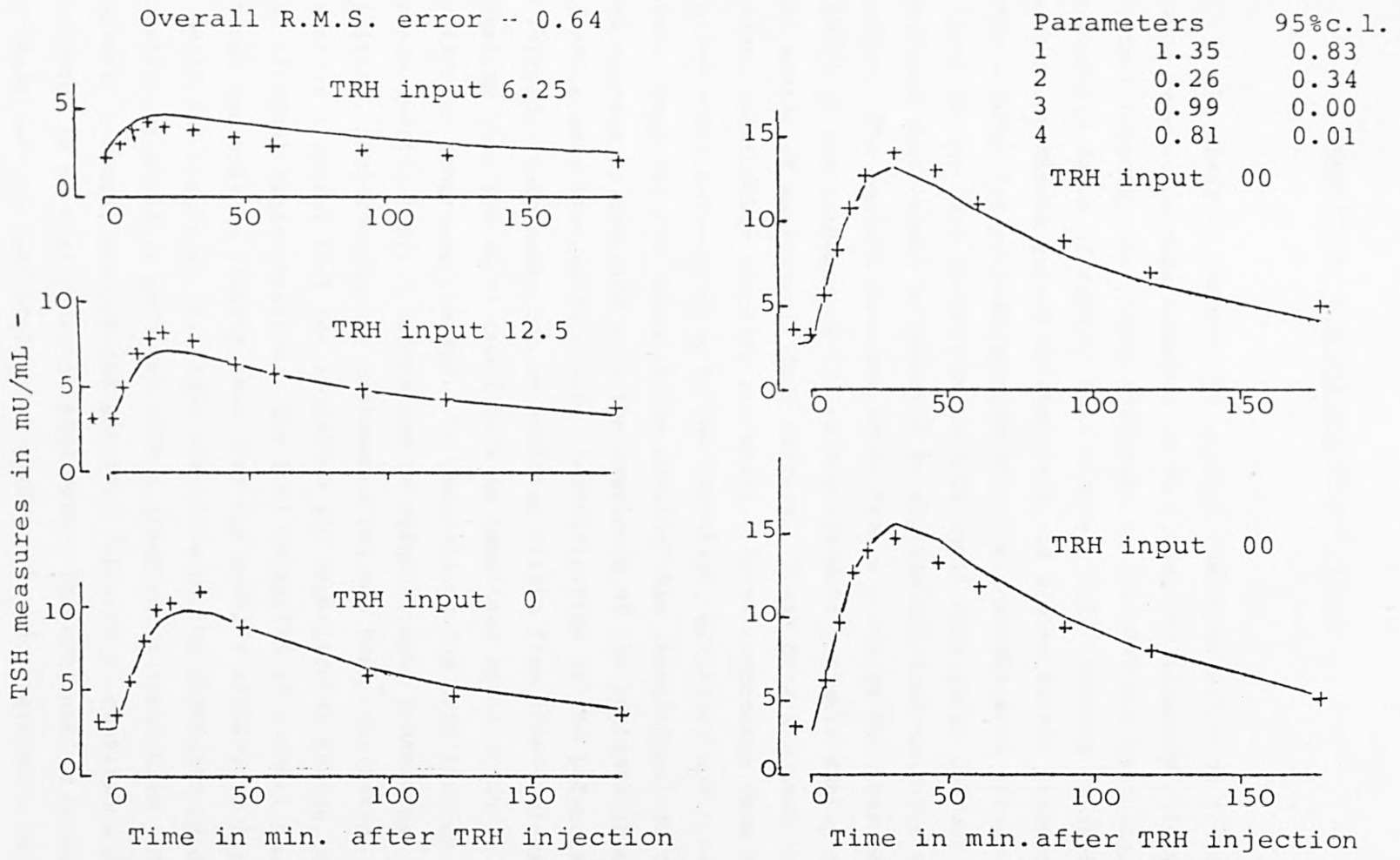


Pituitary response to TRH described by a second order model Figure 6.13



Discrimination of dirders by parameter estimation

Figure 6.14



Fit of 4 parameter difference model of pituitary response to data from Snyder et al
Model parameters are identified on all data simultaneously Figure 6.15

CHAPTER 7

A Clinical Model of Hyperthyroid Patients Receiving Anti-thyroid Drug Therapy

In the previous chapter the general characteristics of thyroid hormone regulation were examined in an attempt to identify clinically important aspects. It proved difficult to discriminate usefully between the possible forms of model. This chapter, while drawing extensivly from the experience gained in chapter 6, is a more direct attempt to derive a model for patient management. The comprehensive structure outlined in the last chapter is reduced until only those featues of behaviours which would be observed by routine clinical measures are included. The patient data are taken from a study by Mortimer et al(1977) of the response of twelve hyperthyroid patients during the first months of antithyroid drug therapy. These data are used to validate and further simplify the model. Three components form the complete model corresponding to the thyroidal, pituitary and tissue systems respectively. Despite the considerable simplifications the model appears to describe well the responses of the patients observed in this admittedly limited data set. Identification of the parameters of the thyroidal components can be achieved within five observations suggesting that the model could have an immediate application in the selection of long-term therapy. To demonstrate the practicality of this approach despite limited laboratory or clinical data processing facilities, a micro-computer implementation has been undertaken. This is seen as a useful tool for education and experimental design, not as a final clinical implementation. The full potential of a model based approach can only be clearly seen when the model's ability to integrate the noisy and scattered data made available to the physician into a comprehensive whole is combined with a graphical presentation. Unusual responses, abnormal results and possible failures of compliance can be highlighted in an easily assimilated form. The conjunction of clinical data-bases and low cost processing power with modern graphics facilities will inevitably lead to the introduction of models to assist interpretation. This chapter is a demonstration of the contribution

which modelling and identification techniques can make even when knowledge of the underlying system is restricted.

7.2 Previous Work on the Modelling of Chronic Disorders

In acute care, or indeed whenever a high data rate and difficulty in discrimination coincide, model based techniques have been adopted as part of any significant data-processing effort. In contrast, there are relatively few routine "on-line" applications of models to the therapy of longer-term, chronically unwell patients. This is despite the numerous references in the modelling and systems literature to the physician-patient relationship as an example of a control system and considerable interest in models for the analysis of clinical data. Petrovski (1974) and Mak et al (1980) have discussed, in general and largely theoretical terms, the derivation of cost functions and their use with state estimation to improve therapy. Gheorghe et al(1976) have taken a rather novel approach through the use of state transition (stochastic) models for the observation ,the underlying dysfunction and the therapy applied. Neither of these approaches has been introduced into clinical practice. In the first case realistic definitions of cost functions and identification of model structure are avoided. The second approach relies heavily upon knowledge of transition probabilities some of which may not be directly observable. It also requires that there are underlying discrete states or faults which may not be an appropriate description of disorders such as thyroid dysfunction, which appear to show a progressive onset. While such continua may be assumed discrete for some purposes, this appears to be an artificial construct for thyroid disease.

Mak et al(1980) have used the model of thyroid hormone distribution and disposal developed by DiStefano et al, (1975) to take a much more direct approach to derivation of "optimal" replacement dosages of T4 for hypothyroid patients. The aim was to obtain the T4 dosages required to restore the patient to the "normal" range according to two criteria. The first was the minimum time to establish "normal" thyroid hormone concentrations without an overshoot and the second was the minimum dosage required to achieve normality in a given period. In each case the clinical state was assumed to be a function of the thyroid hormone

concentration within the tissue compartment and not the plasma level as is usually assumed. As a study to determine the general form or profile for an ideal replacement dosage and to check for possible discrepancies between the tissue and plasma concentrations, this aims to make a contribution to clinical decision making. Unfortunately these problems seem to be secondary to the difficulty in evaluating the normal replacement dose of T4 for an individual patient as discussed in chapter 5. As described in chapter 6 the changes in the T3/T4 ratio observed by ourselves and Ingbar(1982) are not seen in the model used by Mak et al. The critical area of uncertainty is therefore the relationship between the clinical state of the patient and the available measures of plasma T3 and T4. Increased knowedge of the thyroidal secretion rates and peripheral T4 to T3 conversion will allow this model to include these effects but clinical confirmation of predictions remains the final criterion of validity. Indeed, unless it is possible to show that only a few of the 16 parameters in this model vary significantly between individuals it will be impossible to tune the model to particular patients with any degree of confidence. Mak used parameter estimates derived from three normal individuals together with several assumptions in order to identify the model fully. It is not certain that a linearised model identified over a limited range of conditions can be extrapolated to describe the wide transitions seen in unwell and treated patients. Mak's study was an attempt to test and to provide improved criteria for therapy selection by the use of a model of hormone delivery to tissue. In aim it was similar to earlier work which had been directed towards the optimisation of ablative doses of radioactive iodine. Approaches taken ranged from the use of multivariable analysis through to dynamic models of the iodine cycle. The aim was to reduce the incidence of repeated doses or subsequent hypothyroidism. Little improvement could be shown as neither the general characteristics or the dependences upon individual variations could be predicted with sufficient accuracy. This emphasises a common problem in many areas of medicine. The general response may be well established but individual variations cannot be predicted other than by trial and error. To some extent this leads to the "cybernetic" model of therapy. If a response can be approximately described by a first or second order model with noise then the identification of this simple model may be more useful, as a means of smoothing noisy data, than an attempt to introduce a

complex though perhaps more accurate and physiologically based form. An extreme example of this approach is seen in some time series econometric models where the model structure is entirely empirically derived with little or no prior knowledge. Medical practice, however, requires models which include as much prior knowledge as possible but are sufficiently simple to allow identification of individual characteristics with the routinely available clinical measurments. Consistently, as has been discussed earlier (chapter 3), the problems in these applications lie in the implementation of sufficiently robust and efficient measurement systems rather than the particular control algorithm. In particular it must be possible to show that a model-based approach can make some overall improvement in health care or, at least, a significant saving in costs. Earlier chapters have argued for and reported experiments on a system for the routine collection of patient thyroid hormone data. The aim of this chapter is to show that such data can be clinically useful if combined with even a simple and incomplete model of the patient.

7.3 A Clinical Model for Antithyroid Drug therapy

In chapter 6 an attempt was made to identify a quite comprehensive range of the components of thyroid hormone regulation. Only limited success was achieved. The model for distribution, binding and de-iodination could not be fully resolved and in particular the possibility of non-linear de-iodination of T4 was not confirmed. This carries with it implications for modelling the thyroid gland itself as the thyroidal response is observed largely via plasma hormone measures. It does seem clear, however,from empirical evidence quoted in chapter 6, that the gland's response to TSH or to antibodies and the resultant changes in the relative secretion rates of T4 and T3 must be considered linear. Consideration of hormone dynamics with a measurement rate no higher than weekly leads to the elimination of most of the distribution compartments for T4 and T3. Indeed when patients are not receiving T3 it is reasonable to ignore T3 dynamics altogether. This leaves the structure for production and distribution as shown in figure 7.1 where T3 plasma levels are assumed to be proportional to plasma T4. The thyroid gland is included as an "iodoprotein" pool to represent colloidal stores which can be expected to give rise to a delayed plasma

hormone response to antithyroid drugs. Even with a structure as simple as this, the patient will usually be several weeks into therapy before the number of measures significantly exceeds the number of parameters. Drug effects are included by a single exponential inhibition of iodoprotein production rates. This is largely chosen because of lack of detailed knowledge of the absorbtion and metabolism of carbimazole and the need to avoid convergence problems encountered with hyperbolic functions. A saturation in the steady-state response to carbimazole and other blocking drugs in antithyroid therapy has been demonstrated (Taurog , 1978). Physicians at the Middlesex Hospital have also reported cases of an apparent delay,due either to resistance to the drug or possibly a trigger level, before certain patients, usually long-term hyperthyroid patients, show any reaction to these drugs. This effect is poorly documented but seems restricted to a small group of patients. If more data become available, discrimination of this type of patient could be a useful application of patient models.

Once variance in the T3/T4 ratios has been assigned by an analysis of varience to individuals, the small residual shows no further dependence upon drug or TSH levels, though the first measures,before therapy, are associated with higher T3/T4 ratios. The factors discussed above lead to a reduction of the thyroidal and distribution models of chapter 6 to the clinical formulation below:

$$GTH(k+1) = P_1 . e^{[\,P_4 . U(k)\,]} + P_2 . GTH(k) \qquad (7.1)$$

$$PT4(k+1) = P_6 . GTH(k) + P_5 . PT4(k) \qquad (7.2)$$

$$PT3(k+1) = P_3 . PT4(k) \qquad (7.3)$$

Where: GTH(k) Glandular iodoprotein levels at time k
PT4(k) Plasma T4 levels " " "
PT3(k) Plasma T3 levels " " "
U(k) Antithyroid drug taken " " "
P_1 to P_6 Parameters

The lack of any significant change in the T3/T4 ratios of these patients implies that antithyroid drugs block the sensitivity of the gland inputs equally to both antibody and TSH stimulation. This allows the thyroid and pituitary responses to be examined independently during the drug blockade. In the longer term, the supression of the pituitary response and varying of thyroid hormone levels during therapy mean that the return of regualation can probably only be determined by a normal TRH stimulation test. As discussed in chapter 6 it is difficult to separate pituitary effects arising directly from changes in hormone levels from those which may be mediated through hypothalamic response (TRH). This can be complicated further in the long-term hyperthyroid patient by an apparent suppression of the pituitary even after normal or low thyroid hormone levels are achieved. It was expected from clinical measures that a response of power greater than exponential would be required to generate the high TSH values commonly seen after low thyroid hormone levels. The half life of TSH, though uncertain, is of the order of an hour so its dynamics would not appear significant. However, the measure available is actually the TSH concentration occurring 20 minutes after a TRH injection. Linear models by Okano et al, (1978) argue that peak and basal levels of TSH will be proportional while the form of the pituitary response is consistent. In those cases where both basal and peak TSH had been measured an approximate proportionality did seem to hold. Again the simplest possible formulation was sought. Exponential and hyperbolic forms were compared which would give the required long-term changes in observed TSH levels. It should be stressed that the parameters of these models describe changes in the rates of formation of TSH rather than the short term plasma dynamics.

$$PTSH(k+1) = P_1 \cdot e^{[P_2 \cdot PT3(k)]} + P_3 \cdot PTSH(k) \qquad (7.4)$$

$$PTSH(k+1) = \frac{P_1}{PTSH(k)^{P_2}} + P_3 \cdot PTSH(k) \qquad (7.5)$$

where: PTSH(k) = plasma TSH concentration at time k

PT3 (k) = plasma T3 concentration at time k

P_1 to P_3 are paramters

Clinical state recorded as a Wayne Index (Wayne et al, 1952) was even less well founded than the TSH or thyroid hormone structures. Information on even the simplest component of the index as a function of hormone levels is sparse. The kind of extreme individual variation seen in the original data presented by Wayne et al also appears in the Wayne Index measures presented by Mortimer et al (1975). Figure 7.2, however, demonstrates that this confused picture can be resolved considerably when individual responses are followed. It seems clear that saturation of the clinical state outside "normal" hormone levels will occur in most patients and that a swift return to biochemical normality may be accompanied by a pronounced lag in the clinical response. This gives rise to the curved trajectories seen in figure 7.2 of the Wayne Index against the T4 measures. Two simple and completely empirical forms were chosen to exhibit both lag and saturation.

$$CS(k+1) = \frac{P_1 \cdot PT3(k)}{[P_2 + PT3(k)]} + P_3 \cdot CS(k) \qquad (7.6)$$

$$CS(k+1) = P_1 \cdot e^{[P_2 \cdot PT3(k)]} + P_3 \cdot CS(k) \qquad (7.7)$$

where : CS(k) = Wayne Index estimate of Clinical State at time k

PT3(k) = plasma T3 concentration at time k

P_1 to P_3 are parameters

7.4 Identification of the Thyroidal Model

As the individual components are largely independent, the thyroidal,pitiutary and clinical sections can be decoupled and examined in turn. In each simulation the initial state of the model was obtained

from the first measurement of clinical and biochemical variables with any missing observations being calculated using the model with the current parameters. This forces the fit through these first measures, effectively weighting them very heavily. To reduce this effect, the model was started from time t = -40 weeks . This both de-emphasises the first measures and ensures that the model is stable in the absence of a treatment input. The parameter estimation process was repeated using several different initial sets of parameter values to check for convergence.

The parameter optimisation program has previously been applied in chapter 6 and is described in greater detail in Appendix I. All plots shown here were obtained directly as output from this program.

The full model of equations (7.1) to (7.3) cannot be completely identified for this input data when the measures are limited to the plasma T4 and T3 pools. Convergence could be obtained by either assuming a fixed thyroidal T4 secretion rate (parameter 6) or plasma loss rate (parameter 5). This required the simultaneous estimation of 5 parameters.

The results seen in figures 7.3 and 7.4 were obtained by setting parameter 6 to 1.0 and estimating the remaining parameters on the whole patient set. This gives 'typical' values for the parameters and is refered to as a group estimate as distinct from parameter estimates obtained upon data from each individual patient. Each plot shows the T4 and T3 data together with the responses of the model to the changing carbimazole therapy. In figures 7.3 and 7.4 the therapy input has been added to the graphical output from the program as a sequence of solid blocks. The dosage can be obtained by multiplying the reading at any time by 50 to give mg per day of carbimazole. Unfortunatly, as can be seen in these two figures, the inclusion of the therapy data tends to cause confusion and for this reason was excluded from the graphical output. The therapy input has not been changed in subsequent simulations so it has not been added to the remaining plots presented here. While the overall qu ity of the fit may be seen in these plots the exact values are difficult to read. The entire data set has therefore been added at the end of Appendix I. As the parameters are

the same for each simluation, the initial T4 and T3 values at the start of the therapy are also the same. Parameter 3 which defines the T3 to T4 ratio is slightly greater than unity indicating that the normalisation of the T4 and T3 measures was not exactly correct. As a consequence the T3 and T4 responses do not quite overlap. The upper line represents the T3 response. There appears to be qualitative agreement for most patients with patients 5 and 9 showing the most anomalies. Convergence was successful from a range of initial estimates. This confirms the negative estimation of parameter 5 giving an unstable and non-physical model. An attempt to estimate parameter values for each patient was less robust. Figures 7.5 and 7.6 show the results for 100 iterations of the fitting routine from a particular set of initial parameter values. The fits obtained for the first six patients are good (figure 7.5). The data for patients 9, 10 and 12 are, however, not well described (figure 7.6). A change of initial estimates gives a considerable improvement in the fit to these three patients without worsening the results for the other patient data (figures 7.7, 7.8). Unfortunately the responses for patients 3,5,10 and 12 show sharp, unphysiological changes or oscillations which suggest underdefinition of the parameters. The alternative form which fixes the apparent plasma half-life of T4 was identified with parameter 5 now switched to describe the thyroidal secretion rate and the plasma loss fixed at 0.5 which gives an effective half life of 7 days. There was difficulty in obtaining a reasonable convergence even for the whole group of patients. Figures 7.9 and 7.10 show the results after 100 iterations for this form. The poorer fit might be explained by a reduction of the T4 half-life reported in hyperthyroid patients. As treatment proceeds this parameter may therefore change in step with the disappearence of the hyperthyroid state. An attempt to combine these two parameters to give a lower order problem for optimisation is shown in figures 7.11 and 7.12. The effective half life of T4 was reduced (parameter 7 = 0.45 in equation (7.2)) and the input of thyroidal T4 was fixed at 0.5.

This was more successful, but as only three patients appeared to show a lag in their response to carbimazole, the intrathyroidal storage compartment was removed reducing equations (7.1) and (7.2) to:

$$PT4(k+1) = P_1 . e^{[P_4 . U(k)]} + P_2 . PT4(k) \quad (7.8)$$

Figures 7.13 and 7.14 show the optimal responses obtained by fitting the whole group simultaneously. Figures 7.15 and 7.16 show the optimal responses by fitting for each patient. Comparison with figures 7.3 to 7.8 show that the reduction in parameters produces little worsening in the fit with a significant increase in the robustness of the estimates. The individual patient optima can now be obtained even from poor initial estimates. This also suggests that identification on the basis of a usefully small number of observations will be possible.

The table of figure 7.29 summarises the results of these estimations. Individual estimates for each patient gave an average error of 16% for the T4 and 24% for the T3 measures over the whole set of patients. This seems comparable with the precision of the T4 and T3 assays at this time - though quality control information is not available. An indication of the variance in the responses associated with the estimates of parameter uncertainty can be obtained from the program. In figures 7.17 - 7.20 the 95% confidence limits are plotted against the measured T4 and T3 values. For clarity each variable is plotted separately. Note that these limits are an expression of the uncertainty in the overall fitted response and not the likely spread of singleton measures. The envelope corresponds to the uncertainty in the fitted response much as the standard error expresses the uncertainty in an estimate of a sample mean. These plots show the systematic error in the fit obtained for patient 9 very clearly. These results are examined in more detail in section 7.5.

Attempts at further simplification were initially less successful. A linear dependence upon the carbimazole dosage would make sequential estimation much easier. Unfortunately when the linear formulation:-

$$PT4(k+1) = P_1 + P_2 . \log[U(k)] + P_3 . PT4(k) \quad (7.9)$$

- was tried,a poorer fit was obtained in every case (see figure 7.21).

If however parameter 4, which describes the drug sensitivity, was fixed at the group mean (0.081) and the remaining three parameters estimated for individual data then results comparable with the 4 parameter form are obtained. Figures 7.22 and 7.23 show the individual estimates obtained. The group estimates would of course be identical with the 4 parameter form. The corresponding variances in the T4 and T3 responses can be seen in figures 7.24 - 7.27. An overall reduction in the acurracy of the fit obtained for individual estimates increased the T4 error to 20% and the T3 error to 27% (see figure 7.29). It should be noted that the use of the group estimates for parameter 4 will favourably bias the subsequent estimates. An unbiased method of testing the reduced form would be to estimate the group parameters excluding each patient in turn. The group estimates could then be used to give the fixed parameter value(s) for the individual estimates using the reduced form. This is an extension of the 'leave one out' technique used in discrimination and pattern recognition studies.

A more direct route for model reduction would have been to examine the existing parameter estimates. A parameter with relatively small variability or which had wide confidence limits would be a possible candidate. On these grounds fixing first the T3/T4 ratio (parameter 3, variation about 30%) and then the 'loss' parameter (variation about 2 fold) would have been the more obvious sequence for model reduction. The aim, however, is to produce as complete and as readily identifiable a model as possible and the T3/T4 ratio is both relatively easy to estimate and provides an additional source of information to confim changes in patient state. Model reduction therefore is also strongly dependent upon function and measurement. In this case the fixing of parameter 4 produces a linear model with advantages for optimisation. It would, however, be possible to return to these data and re-examine different structures as experience with a wider range of patients became available. This is discussed further in section 7.8.

7.5 Individual Patient Responses

An interesting problem was encountered in trying to fit the data for patient 3. A consistently poor fit was obtained with all models -seen as a high residual sum of squares - and led to a detailed review of the observations made on this patient. As figure 7.5 shows, a relapse in the patient state occurs from about week 12 to week 20 following a gap of some six weeks during which no data are available. No change in the therapy was recorded in the raw data during this period, but it seemed likely that the drug input had been stopped or reduced during this interval. Running the model without therapy input from week 7 to week 12 produced good agreement and parameters much closer to those obtained from the other patients. On checking the paper by Mortimer et al(1975) a reference was noticed to a patient who had failed to comply with treatment for some time after an emotional upset. A process of elimination was then used to confirm that this was a reference to patient 3 in the raw data set. Other similar instances may have arisen among the patients ,such as in patient 4 after week 20, but no further evidence on compliance was availible and no other changes to therapy could be confirmed.

The T3/T4 ratio usually remained quite constant but there were exceptions. Patient 4 showed discrepancies after week 20, Patient 9 also showed interesting changes when the T3 data were compared with the model predictions. Initial relatively high T3 results were terminated by very high 'outliers' at weeks 10 and 15 and followed by a series of seven relatively low T3 results. These results on patient 9 may indicate that in some cases the T3/T4 ratio does not stablise immediately after the start of treatment with antithyroid drugs. The response of this patient was re-estimated with the two 'outlier' T3 measures removed. As figure 7.28 shows, the underlying shift in T3 level remains though the parameter estimates move towards more typical values. The ability to detect and easily retrieve data on such unusual responses is one of the aims of this work.

7.6 Identification of the Pituitary Response

The TSH component of the system is driven by the T3 plasma hormone levels. Simulations could be run by driving the TSH subsystem from either the observed thyroid hormone levels or by using the 'smoothed' thyroid subsystem output fitted earlier to determine any missing values. To ensure the closest correspondence to the observed T3 values the 4 parameter form giving the responses of figures 7.15 and 7.16 was used to 'drive' the pituitary models examined in this section and the models of clinical state in section 7.7. For both of these clinical state and pituitary subsystems the 'group' estimates were made using the T3 outputs from the individually estimated thyroid subsystems. An alternative method would employ the output from a 'typical' patient thyroid subsystem using the responses of figures 7.13 and 7.14. The use of a typical thyroidal response could give a better result if the pituitary or clinical subsystems were characterised by heavy damping or had dominant modes of behaviour which were excited by changes in the thyroid hormone levels. An example of the latter would be a non - linear oscillator whose limit cycle behaviour could be switched by input disturbances. Under these circumstances the nature of these driven components might by seen most clearly by smoothing the noisy input. Although both the TSH and clinical responses appear to show delays there does not seem to be any greater consistency than in the thyroidal responses. The TSH response to falling T3 and T4 levels seems particularly variable. In some cases there is an almost immediate rise in TSH as T3 levels begin to fall, whilst other patients show a delay or continued suppression throughout the course of the therapy. The clinical state, perhaps because it reflects the physician's expectations, appears to be more consistent and an examination of the typical response to an 'average' biochemical development is shown in the next section . In practice, patient management will require the more detailed knowledge of individual behaviour which can only be obtained by repeated observation and identification.

Including those patients who showed no TSH response at all, the results of fitting the two models are given in figures 7.30 - 7.39. Neither of the two model formulations seem completely successful, though the reciprocal form can achieve the greater swings in TSH levels

obtained in some patients. In both cases, however, there appear to be changes which cannot be related to variations in the T3 levels. While patients 1 and 2 show at least qualitative agreement, patients 4, 6, 7, 8 and 9 seem to indicate some periodicity or out of phase effects. This suggests that some more complex form is required, probably mediated through TRH interactions as thyroid hormone levels normalise. Though there appears to be a correlation between the basal and peak TSH levels (after TRH stimulation) this might not be confirmed when they both change over time. Further work should therefore attempt to acquire additional data on the basal TSH changes during carbimazole therapy to test the simple models proposed here before turning to more complex forms. This is becoming more feasible as increasingly sensitive assays for TSH appear. There are insufficient data in this study to test either the basal changes or consider a more extensive pituitary model.

In more detail the typical group estimated responses using first the exponential form (equation (7.4)) and then the reciprocal form (equation (7.5)) appear in figures 7.30 and 7.31 and then 7.32 and 7.33 respectivly.

The individual estimates appear in the next set of figures. The reciprocal fits (figures 7.36 and 7.37) are similar to the exponential fits (figures 7.34 and 7.35). If a power reciprocal form is used then a small improvement is usually possible (equation 7.9 and figures 7.38 and 7.39). The changes are not great and cannot account for the discrepancies noted above. Note that some estimates show values for the TSH "loss" parameter 9 greater than unity. This parameter does not correspond to a true plasma loss but to the ratio of "basal" production to degradation by the pituitary and plasma. If this ratio slowly increases with time then this parameter will be greater than one.

7.7 Identification of the Clinical Response

The saturating hyperbolic form of equation (7.7) gave rise to difficulties in estimation. Convergance to the same values could not be guaranteed and the estimated variance in the parameters tended to be large. The reduced hyperbolic and exponential forms, however, proved more robust giving relatively small variations with a reasonably good

description of the data. The exponential form of equation (7.8) has therefore been used throughout the simulations which follow.

Elimination of the lagged component of equation 7.8 (setting parameter 3 to 0.0) produces a generally poor fit of the data (figures 7.40 and 7.41). As was noted in section 7.6, it is possible to drive the clinical subsystem either by 'typical' T3 responses to therapy or by the observed individual responses. Figures 7.42 and 7.43 show an overall group fit of the clinical response driven by the typical thyroidal response to the various therapies. In figures 7.44 and 7.45 the same group fit has been obtained for the individual responses to therapy. Unexpectedly there is a small worsening of the fit when the individual thyroidal responses are used. This might suggest that the thyroidal data were not a good indicator of the clinical state. If, however, the individual clinical responses are estimated for 'typical' (figures 7.46 and 7.47) and for individual thyroidal responses (figures 7.48 and 7.49) then the 'typical' fits are usually poorer. This indicates that the clinical subsystem itself retains considerable variability which cannot be reduced by simple observation of the T3 levels.

While it seems that these relatively simple and empirically derived models adequately describe the changes in this overall clinical index, it might be argued that the physician imposes some degree of smoothing on the index to obtain consistency with previous clinical and biochemical observations. As a consequence either an ideal objective determination or a subjective evaluation taken from the patient could show disagreement with the reported values of this overall index. Perhaps of greater practical importance for future application is the difficulty of obtaining these index values. The data which could be obtained during the pilot study were much cruder than most of the elements which make up the index. It therefore seems unlikely that the Wayne type of index can be expected to be used for routine consultations. The appearance of the microcomputer might do something to improve this situation. In particular the patient might be employed to supply a subjective self-assessment which, though limited in some ways, would reduce the physician's bias introduced through biochemical information. Nursing staff could also input any routine observations,

such as weight and pulse, made during sample taking. There would still remain a need to validate a model of these clinical observations.

7.8 Sequential Estimation of Clinical Model Parameters

The rate at which sequential measures can improve the estimates of the model parameters is of prime importance in any clinical application. If a model is to be used to predict the maintainance dose, for example, then the model estimates of patient state must be sufficiently close to the final clinically observed values to give correct predictions before the patient actually receives a maintenance dose; that is before the physician establishes by trial and error the correct dosage and without requiring a significantly higher measurement rate to do so. To investigate the rate of parameter convergence the estimation algorithm was used repeatedly with different subsets of the total set of measurements availible on each patient. Measurements after a particular time (i.e. weeks since a therapy began) or after a particular number of measurements were assigned a very low weighting and thus had little impact upon the estimation procedure. Missing values are already weighted zero by the algorithm. The reason for giving a very low, but non-zero weighting to the later measures was to retain a slight constraint on the estimations made on the earlier values. The algorithm is an unconstrained optimiser and in practice some limitation on the possible parameter values is required. No attempt was made to include an *a priori* estimate - say from the mean response of the group of patients - which would help to limit the parameter values obtained from a few noisy samples. Unfortunately the estimates of the confidence limits provided by the program do not take account of weighting values - indeed the program as it stands does not even recognise missing values. The error in the confidence limits due to missing values is normally slight but when a large proportion of the recorded measures are to be ignored the confidence limits are drastically underrated. Rather than modify the algorithm the procedure adopted was simply to repeat the estimation process with the ignored values completely excluded from the data set read by the program. The effect upon the final parameter values was usually slight and the confidence limits were transferred to the original plots of predicted patient response. The plots of figures 7.50 and 7.51 show the estimated responses for the first five measures

only. The increase in error is given in the table in figure 7.29 as rising to 25% for T4 and 36% for T3. It seems therefore that a reasonably good prediction of thyroidal response can be made after only five measures. This is perhaps not surprising if it is recalled that most of the changes in therapy are occurring in this period. These changes may be considered as experimental perturbations by the physician to identify directly the most suitable dosage for each patient. The introduction of a formal identification procedure is an attempt to quantify this process and so establish the characteristics of each patient. These characteristics can then be applied to the interpretation of subsequent observations and to attempts to discriminate types of patient or discrepancies in results.

7.9 A Micro-computer Implementation of a Thyroidal Antithyroid Drug Model

It should be noted that although the laboratory has been seen as the site for implementation of these models, the appearence of low cost microcomputers makes direct clinical access feasible. This in turn allows a much wider range of applications . The physician may, for example, test proposed therapies before recommending them and use the model predictions to suggest the next consultation.

The earlier sections of this chapter have described the identification of a reduced model of thyroidal response to the antithyroid drug carbimazole using an extensive range of software and hardware facilities. The Prime 550 minicomputer supports a number of graphics terminals and both the N.A.G. and GINO libraries. It might be argued that this facility is unlikely to be available even in a comparatively well equipped clinical chemistry laboratory and therefore even the simple models described above cannot yet be introduced to the "on-line" interpretation of results. The recent appearance of powerful low cost micro-computers together with extensive storage suggest that these limitations are unlikely to remain any constraint on implementation in even the smallest laboratory. To show that even with existing hardware these models can be implemented and to demonstrate their potential for interpretation of data, evaluation of therapies and as teaching aids the model of thyroidal response presented here has been

implemented on a micro-computer.

The APPLE II has proved a popular choice within the Middlesex Hospital Medical School for small laboratory data-processing tasks despite the existance of larger local machines and a link to the University of London Computer Centre. In comparison with many contemporary machines, the APPLE II must be considered limited if not already obsolete. The ubiquitousness of the machine - it is found in some 10 to 20 locations through the medical school - suggests that it will remain a local defacto standard for some time. If an even moderately acceptable program can be developed on this machine the potential usage is much greater than a far superior version on a distant mainframe and it is clear that there will be few problems when the next generation of machines become available.

The hardware and programs are detailed in Appendix II. The program allows the loading of patient data, the fitting of the patient model to these data and further simulations with changed data. The measurement error can be incorporated and fitting and plotting of patient response include the expected measurement error.

The program is divided into two modules. PAT.THY.GEN allows assay and clinical data to be input manually or loaded from existing disc files. Data may be checked and edited if necessary before being written to a file for use by the fitting and simulation module PAT.THY.FIT. A limitation of the microcomputer used is a 40 column screen which makes presentation of the data difficult. As a consequence only two sets of measures on a patient can be fitted simultaneously and the results conveniently displayed. In the present case this is not a difficulty as the models used do not fit more than two variables (i.e. T4 and T3). The thyroidal model has been taken as an example and equation (7.8) can be fitted for 1 to 4 parameters as required by the user. The measurement errors would normally be provided with each result but for this example a simple quadratic relationship between error and result is assumed. The user may input parameter values and plot the resulting response on the graphics screen. The estimated T4 and T3 concentrations at each measurement time will appear together with the parameter values and the overall r.m.s. error appear on the separate text screen. The

program allows the user to switch quickly between the two displays (figure 7.52). While the optimisation routine is running improved estimates may be printed out and the user can interupt the routine if desired. After optimisation the new parameters and reponse are automatically printed and plotted. This allows the user to compare the initial reponse, which might be generated from the group parameter estimates, with the reponse obtained after parameter optimisation on the data for a particular patient (figure 7.53). The screen may be cleared at any stage and the current response replotted alone. The user may return to modify the initial data and experiment further with changes in therapy, for example.

A Simplex search algorithm was chosen for optimisation largely because of its compactness and relative robustness. It is however slow in convergence particularly when the number of parameters is greater than two. Running the algorithm in interpreter BASIC on an 8 bit microcan mean delays of several minutes which is unacceptable for interactive users. Experience with users of RIA calibration software has shown that even delays of 10 to 20 seconds can discourage users from experimentation while delays of minutes may inhibit use of the program altogether unless success is certain in a single pass of the optimiser. Interestingly, presentation of intermediate results seems to reduce the perceived time required to reach an optimum. Unfortunately this phenomenon though useful if the program is to be used for demonstration purposes or teaching, is not likely to make the program acceptable for 'on line' applications in a laboratory or clinic. Experience with similar programs suggests that reductions in running time of 4 to 5 fold can be obtained by adding floating point hardware and compilation of the code. A more significant improvement is likely to arise from an algorithm with faster convergence, particularly if it can be tailored to the model used. Unfortunately the hardware and software constraints on this microcomputer also suggest that these improvements would only be obtained at a substantial software cost. A further consideration is the relatively low quality of the graphics and the need for special routines to mix graphics and text.

Implementation on current 8 bit microcomputers appears useful for demonstration purposes but their lack of processor speed and limited

memories exlude an immediate on line application. Machines based upon 16 bit processors and 8 bit memory are becoming available and may be sufficiently fast though there are indications that processing is only marginally faster (15 - 20 %) If this is correct then on line implementation may not be possible until the 32 - 16 bit processors (e.g. 68000) are found in low cost microcomputers. Some examples of this third generation of microcomputers have appeared which include very flexible powerful, graphics orientated operating systems and languages (e.g. smalltalk by Xerox). The availability of such data-processing power at low cost will render feasible 'off the shelf' systems which include local interactive data bases within a clinic or laboratory. Under these circumstances the failure to introduce model based interpretive programs would represent a tremendous waste of resourses.

7.10 Conclusions on the Model Fit to Hyperthyroid Data

A problem with these data from the control engineer's view - though not the patient's - is that the physician tries to minimise control input changes and in particular avoids having to reduce and then subsequently increase therapy. This means that the initial "hunting" period where a control model is generally identified is not only short but frequently monotonic in the control variable. The confidence that can be placed in the parameter estimates is thus limited. There is no guarantee that patients first taken off therapy and then returned to it will in fact behave with consistency. This is of importance when trying to detect remission from disease by detecting a long-term drift in the variables and hence the parameters. The results on the patients taken off therapy do not answer this question since the data are sparse and noisy.

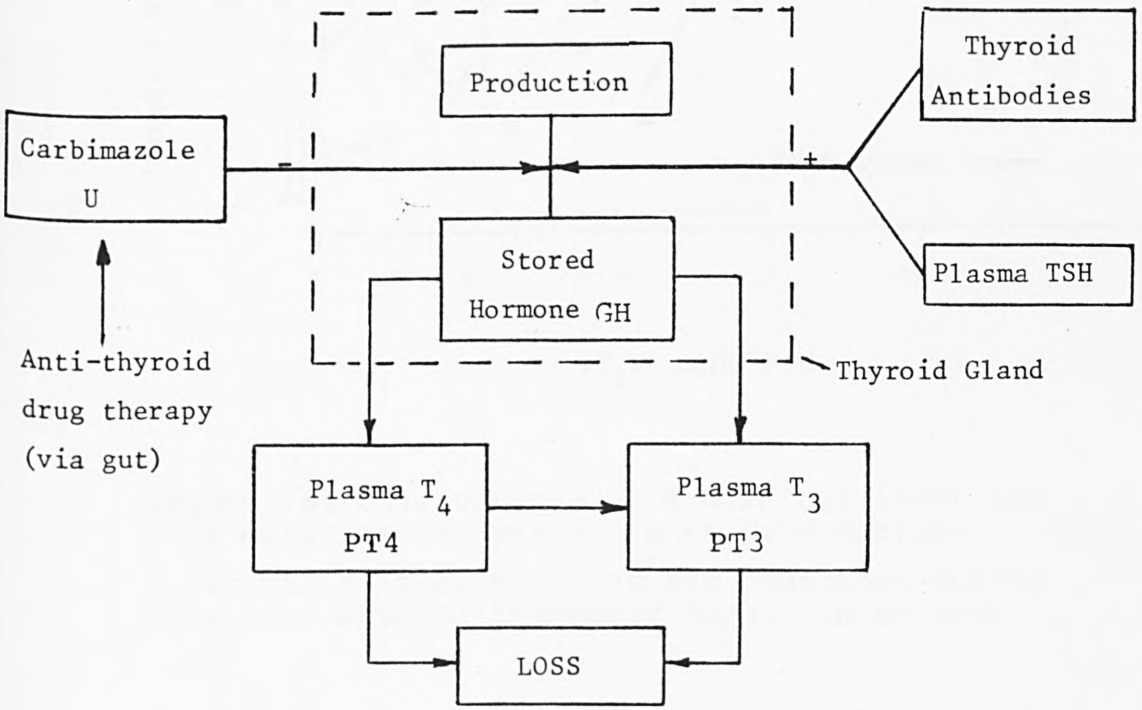
A number of conclusions can, however, be drawn from these data:

(i) A simple model appears sufficient to describe the changes in thyroid hormone level and overall clinical state observed in these patients during therapy.

(ii) The errors in the model fit are comparable with the measurement precision (10 %.) so more complex models would probably only be useful for the pituitary where significant qualitative errors remain.

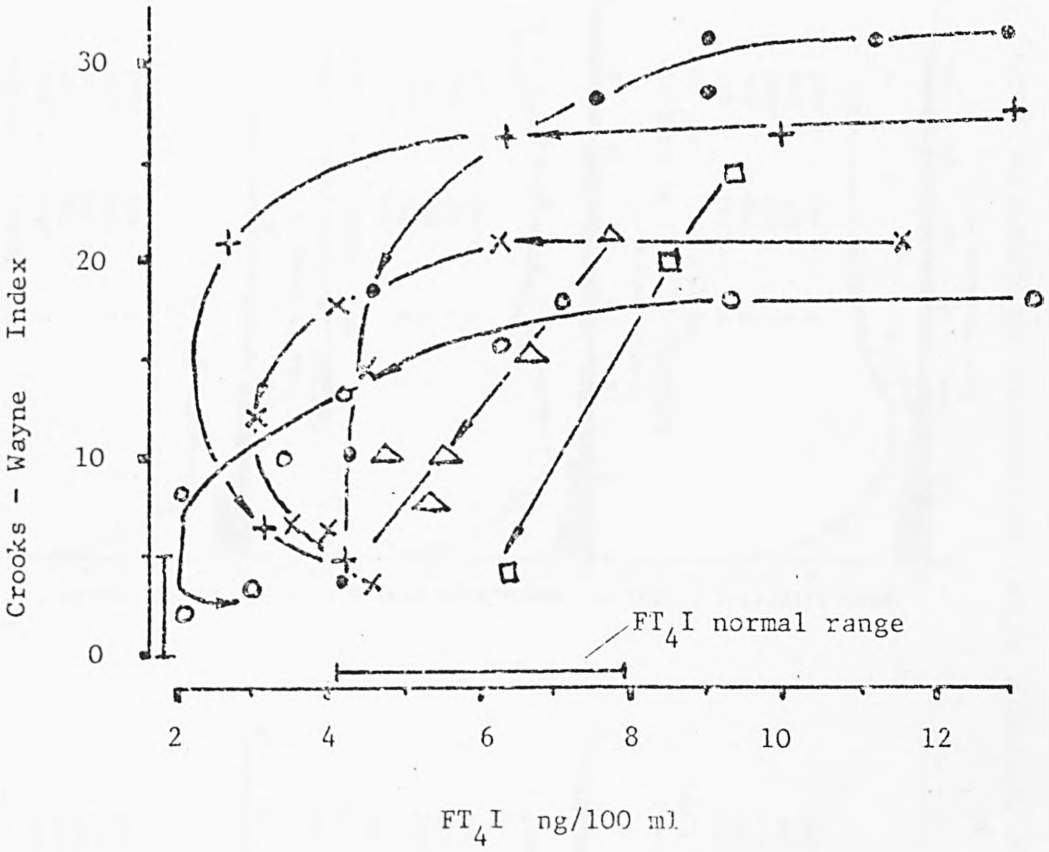
(iii) After the first few observations of the T4 and T3 levels there is little value in determining both as the T3/T4 ratio remains essentially constant throughout.

This final point however ignores the value of the T3 test as a possible test of failure of blocking of the thyroidal response. It should also be re-examined in the light of work by DiStefano (1980) who argues that replication of measures at optimum times will give better identification than the same number of measures taken in sequence.



Reduced clinical model of thyroidal response Figure 7.1

Trajectories through Clinical Index, FT_4I space
for six patients from Mortimer (1977)



Sequential observations of a clinical index and FT_4I measures for six patients from Mortimer

A saturating response, lag and overshoot during treatment with anti-thyroid drugs can be seen

Figure 7.2

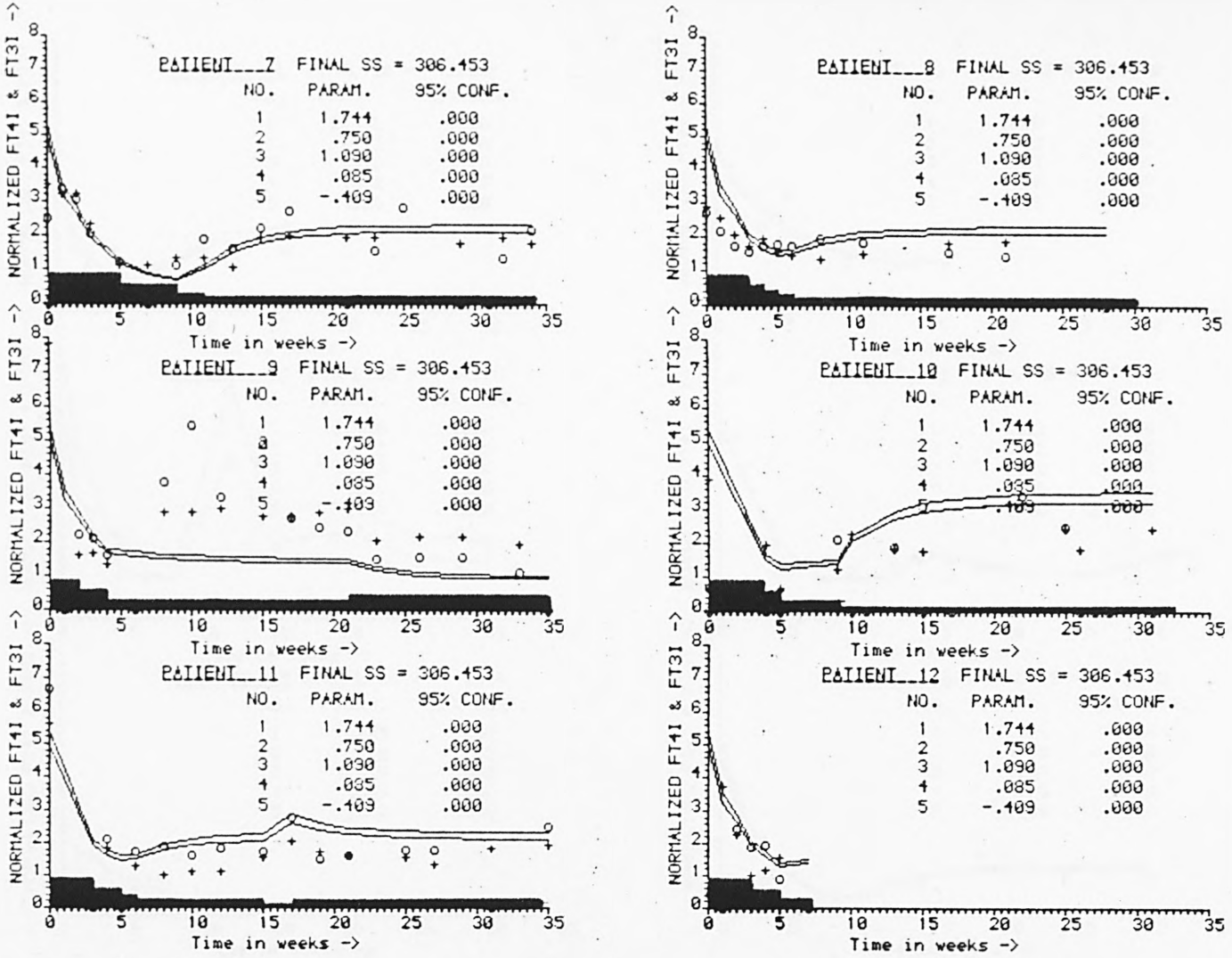
FT4I and FT3I data normalised asdescribed in text

\+ FT4I observations o FT3I observations

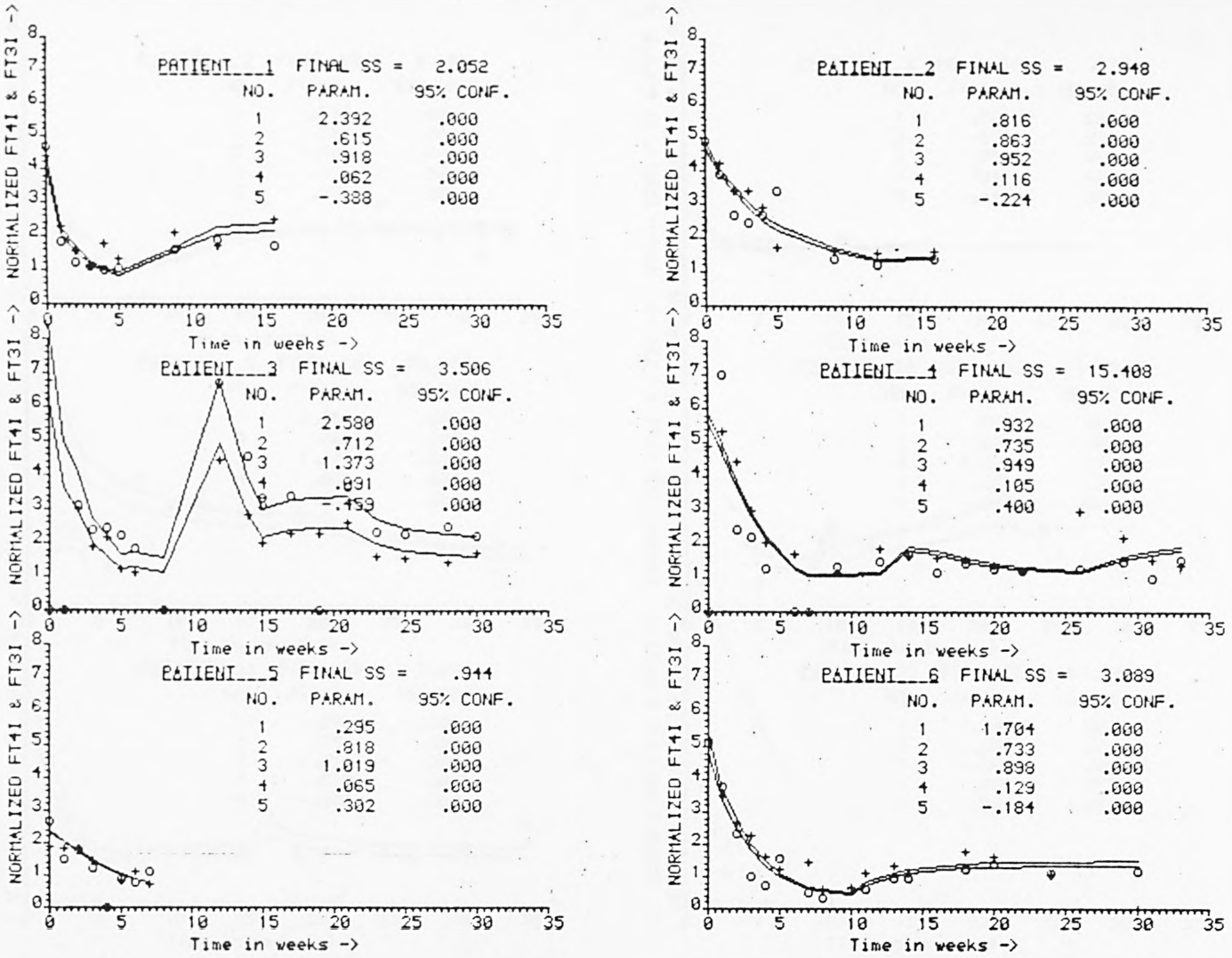
FT4 and FT3 responses to Carbimazole therapy after parameter estimation using the whole set of data from 12 patients (Group estimates)

Figure 7.3

Carbimazole dosages in mg per day can be obtained by multiplying values by 50 . A full listing of all data and input dosages appears in Appendix 1



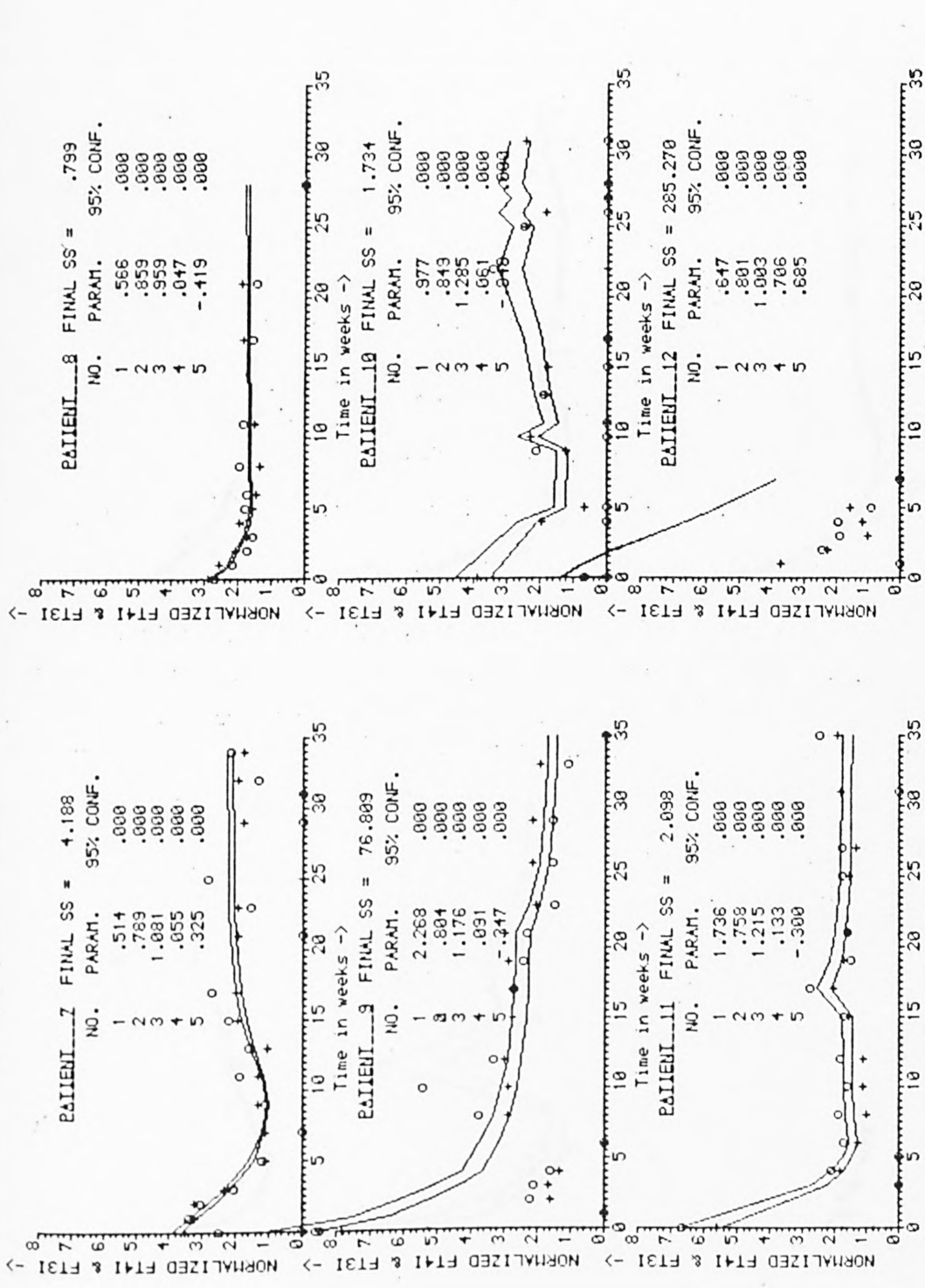
FT4 and FT3 responses to Carbimazole therapy after parameter estimation using the whole set of data from 12 patients (Group estimate) Figure 7.4



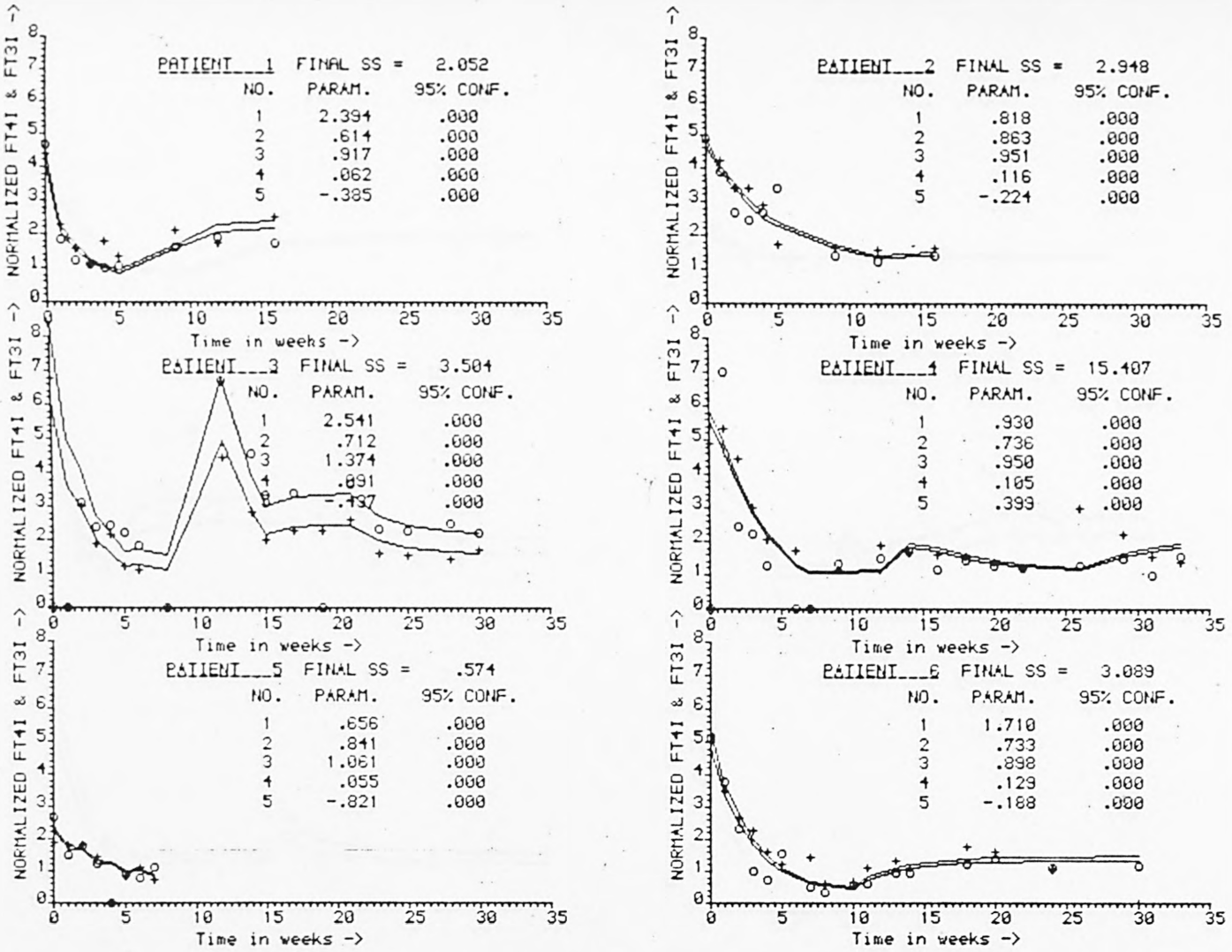
FT4 and FT3 responses to Carbimazole after parameter estimation on each individual patient data set (identification stopped after 100 iterations) Figure 7.5

Note poor initial parameter estimates used to obtain the results in this figure and 7.6

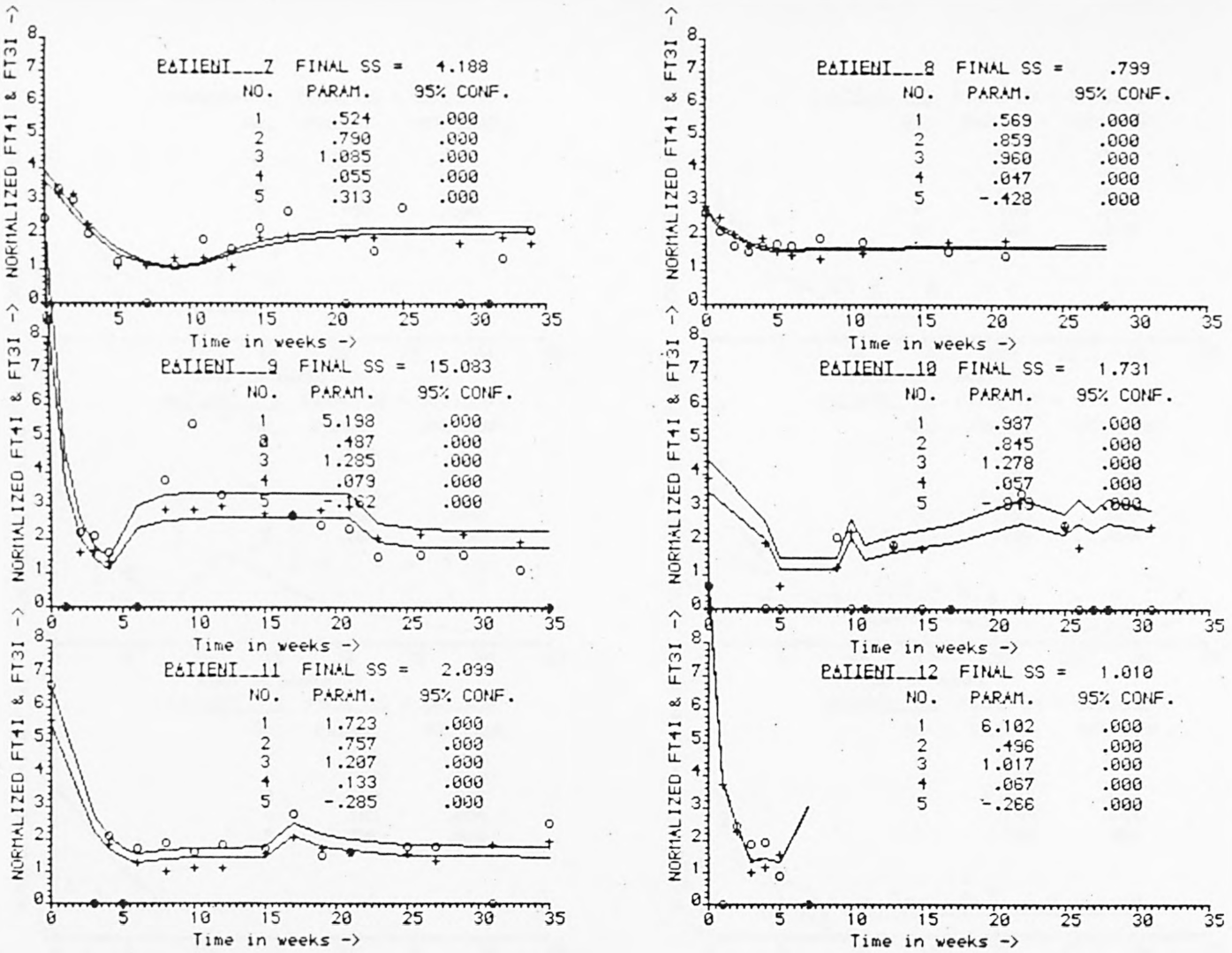
Note failure to converge for data from patients 9 and 12 and oscillatory form for patient 10



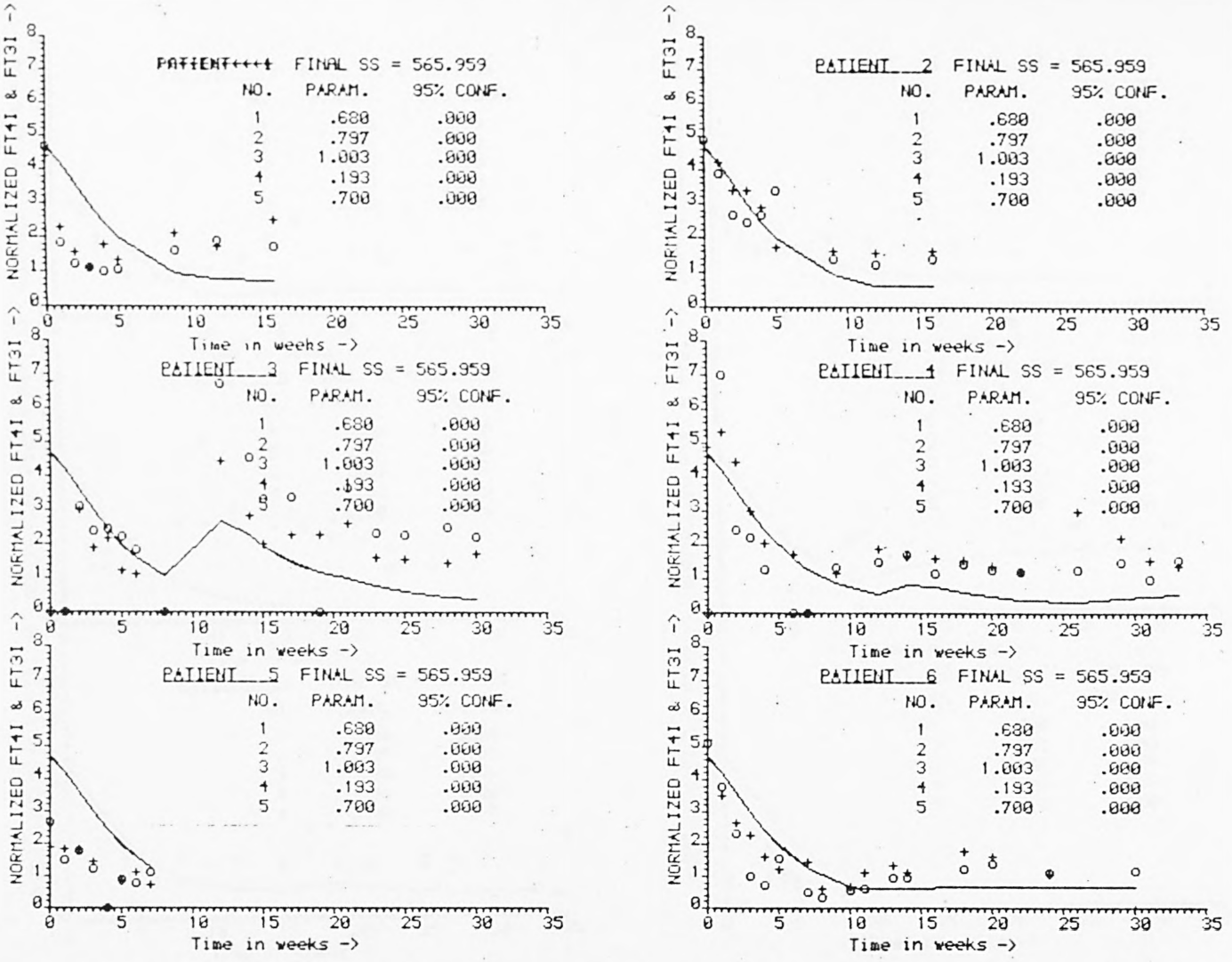
FT4 and FT3 responses to Carbimazole after parameter estimation on each individual patient data set (identification stopped after 100 iterations) Figure 7.6



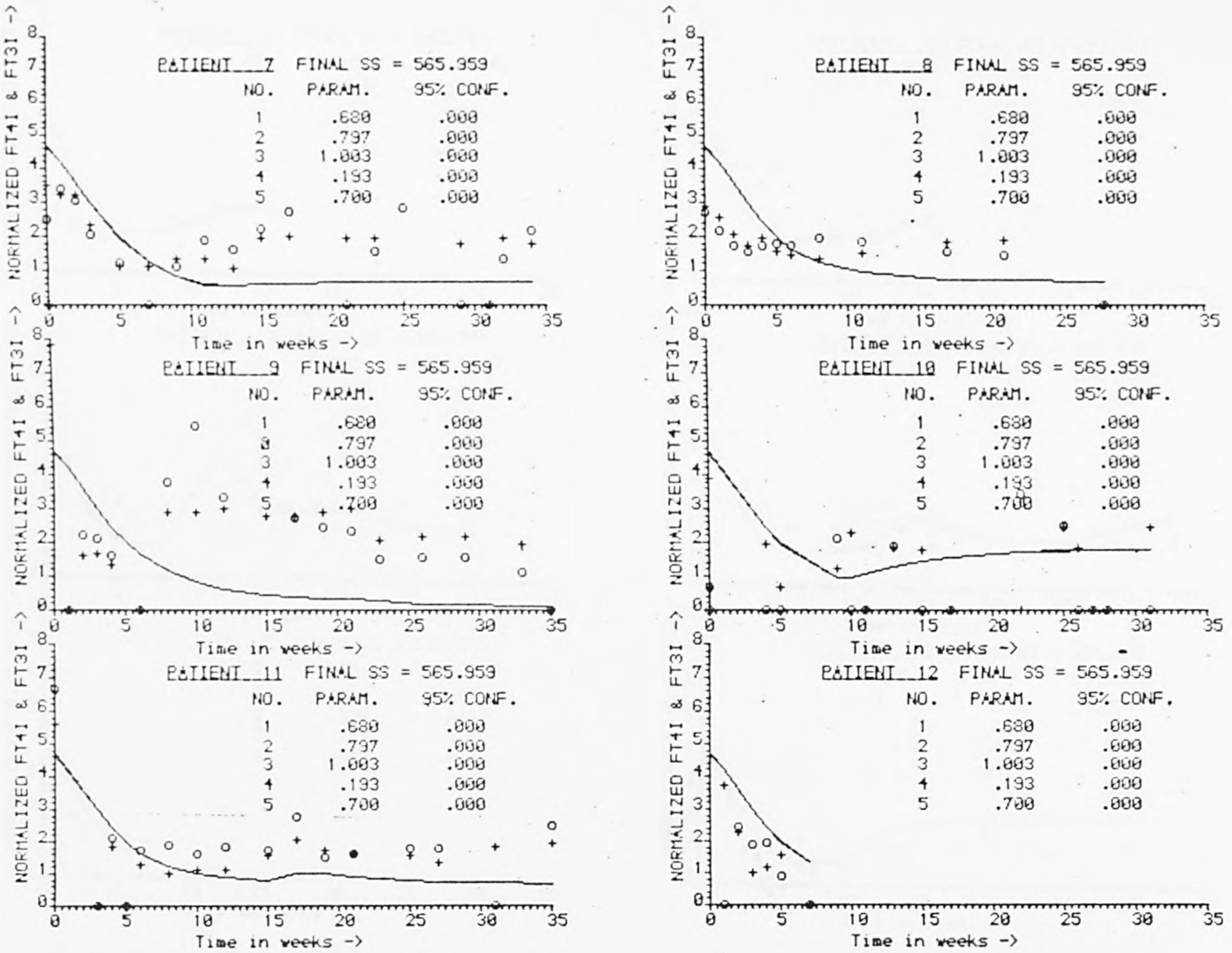
FT4 and FT3 responses to Carbimazole after parameter estimation based on individual patient data using a modified initial parameter estimate Figure 7.7



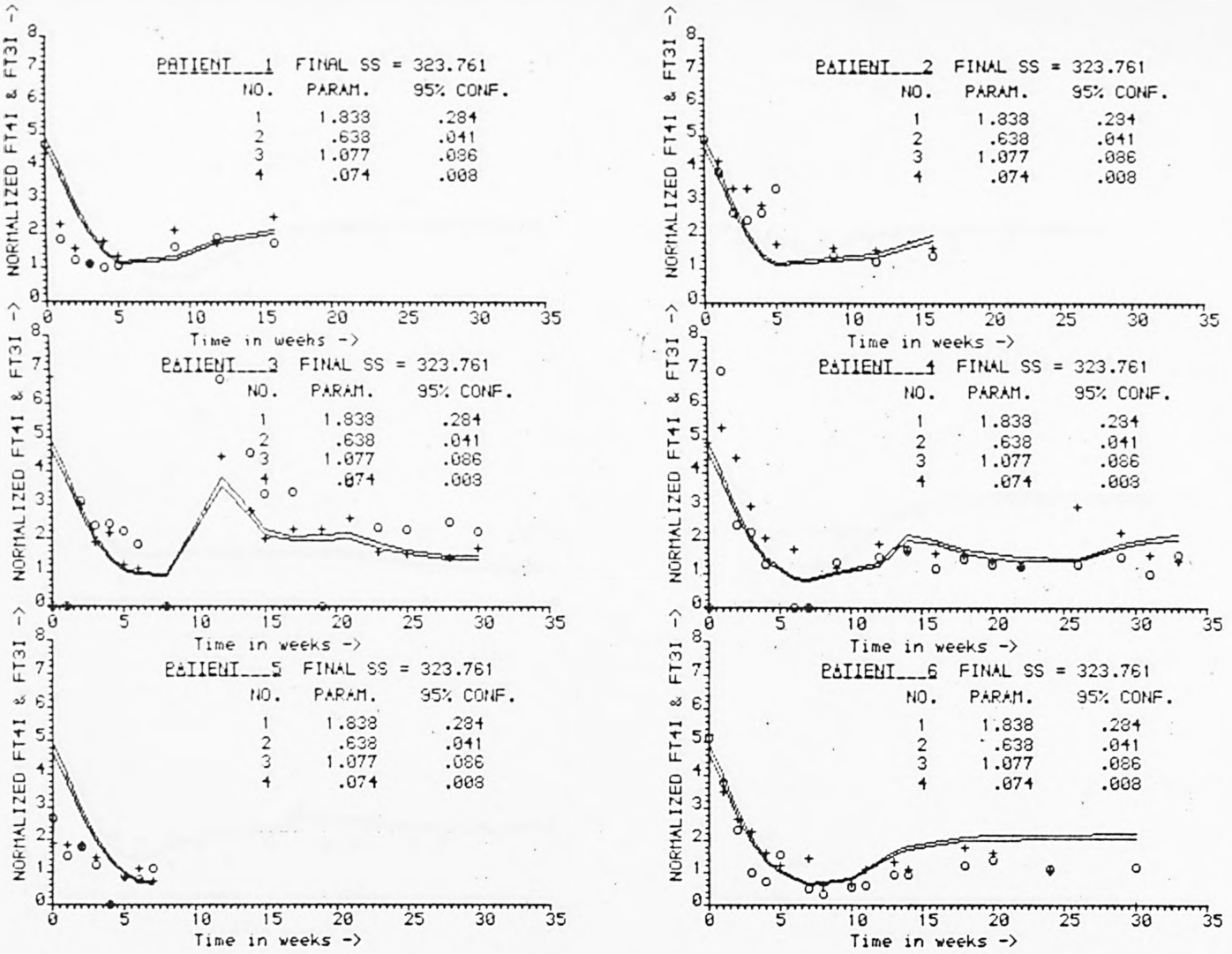
FT4 and FT3 responses to Carbimazole after parameter estimation based on individual patient data using modified initial parameter estimates Figure 7.8



Poor convergence for a group estimation on FT4 and FT3 data assuming a plasma T4 'half-life' of one week (estimation stopped after 100 iterations) Figure 7.9

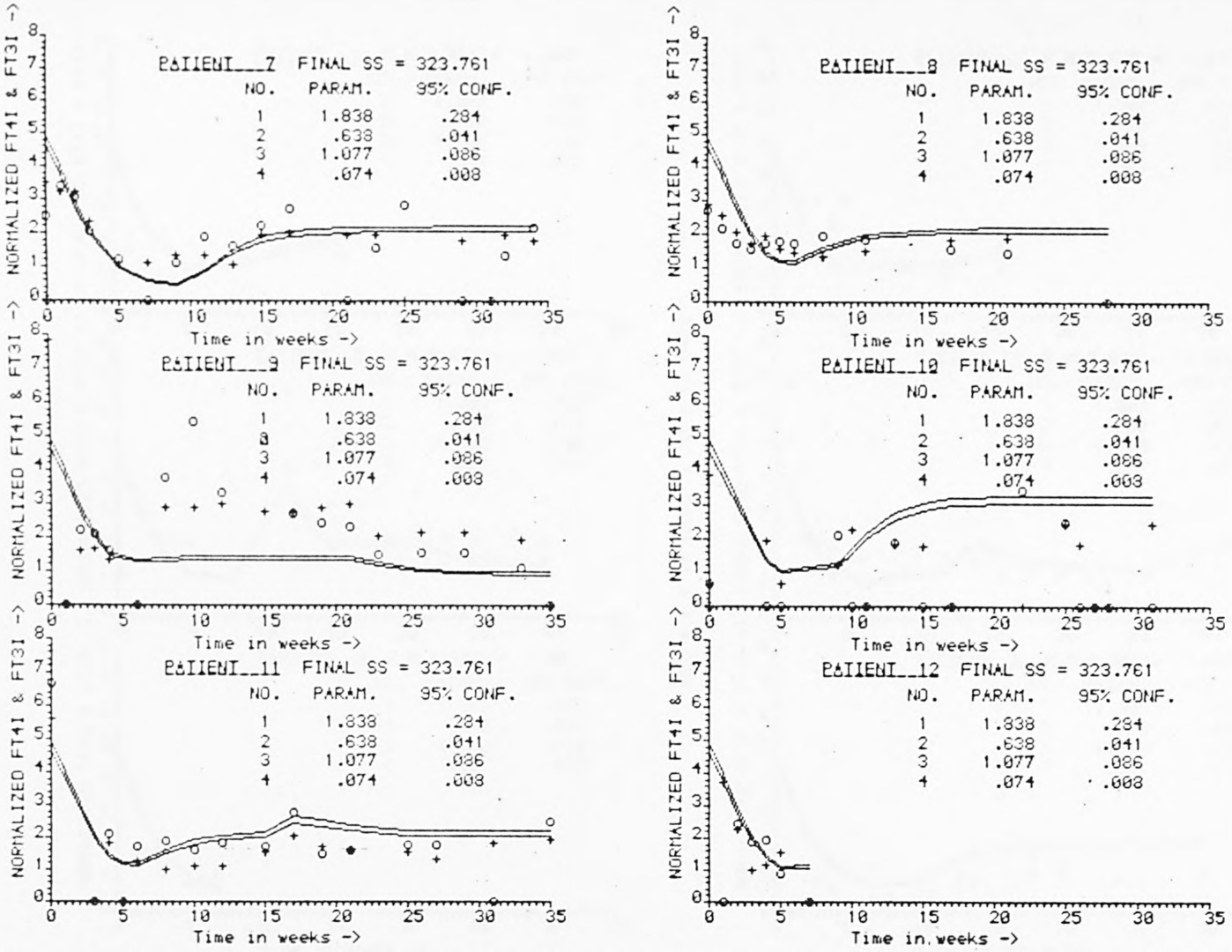


Poor convergence for a group estimation on FT4 and FT3 data assuming a plasma T4 'half-life' of one week (estimation stopped after 100 iterations) Figure 7.10



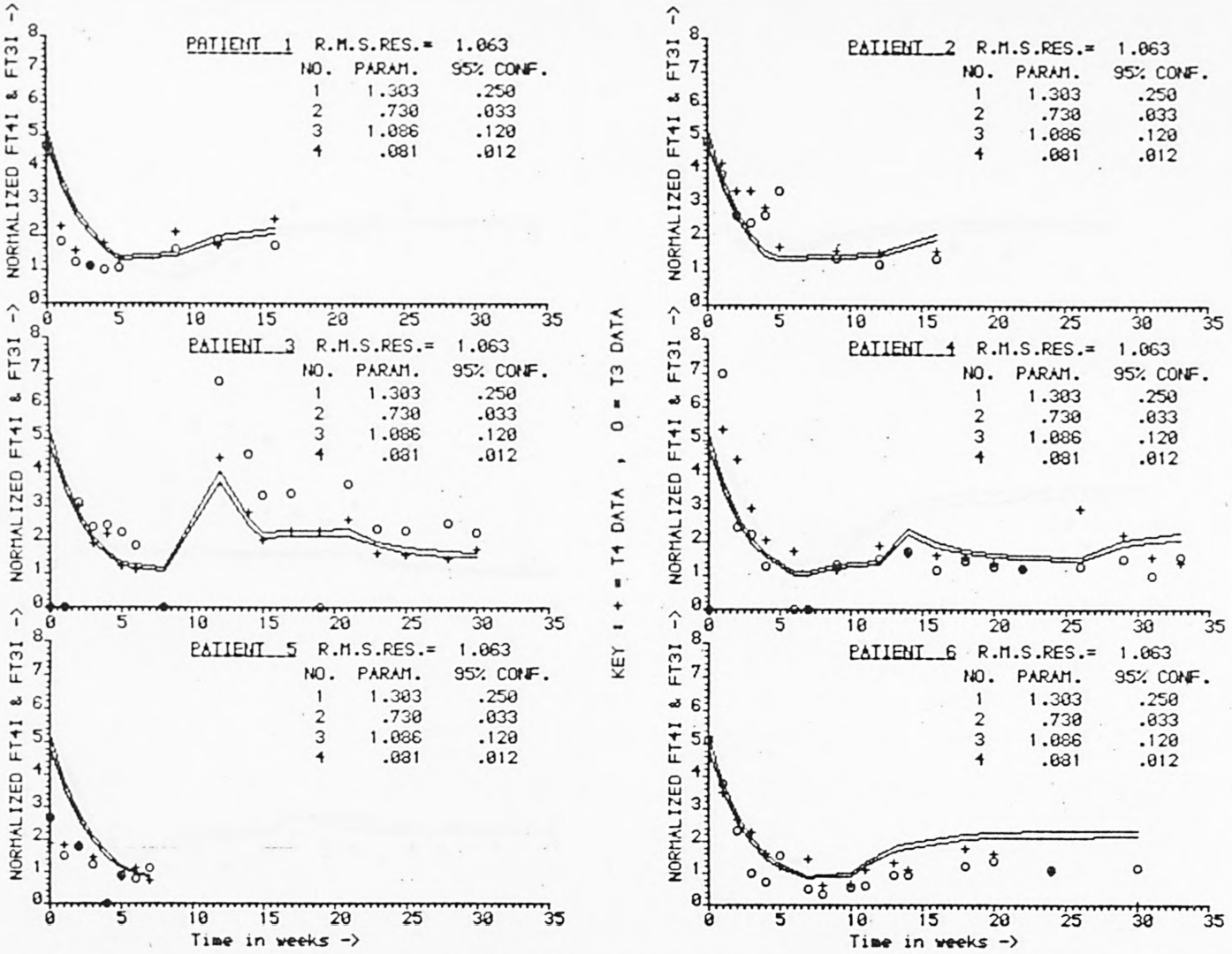
Group fit of thyroidal model with fixed secretionrate and T4 plasma 'half-life' of less than one week

Figure 7.11

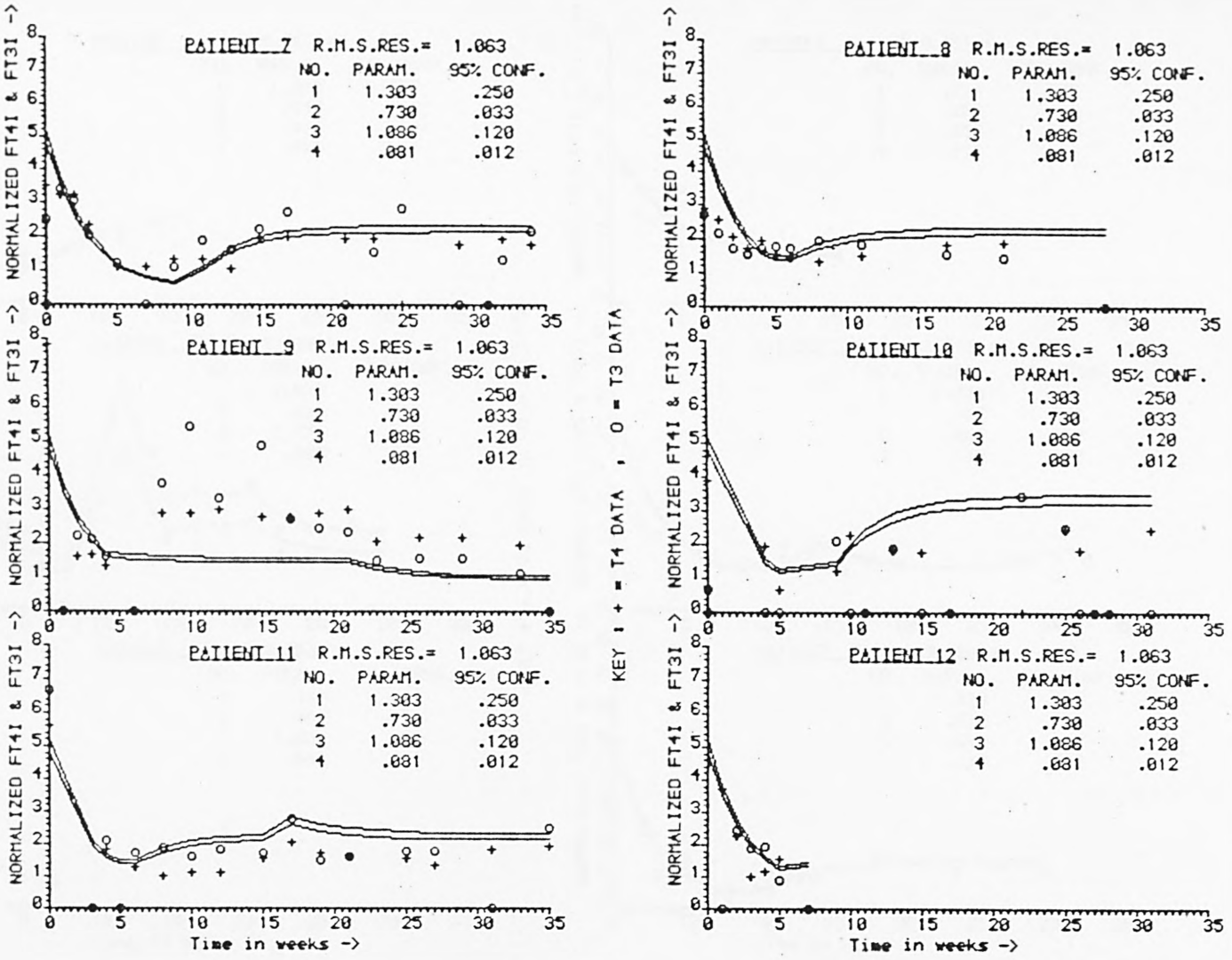


Group fit of thyroidal model with fixed secretion rate and T4 plasma 'half-life' of less than one week

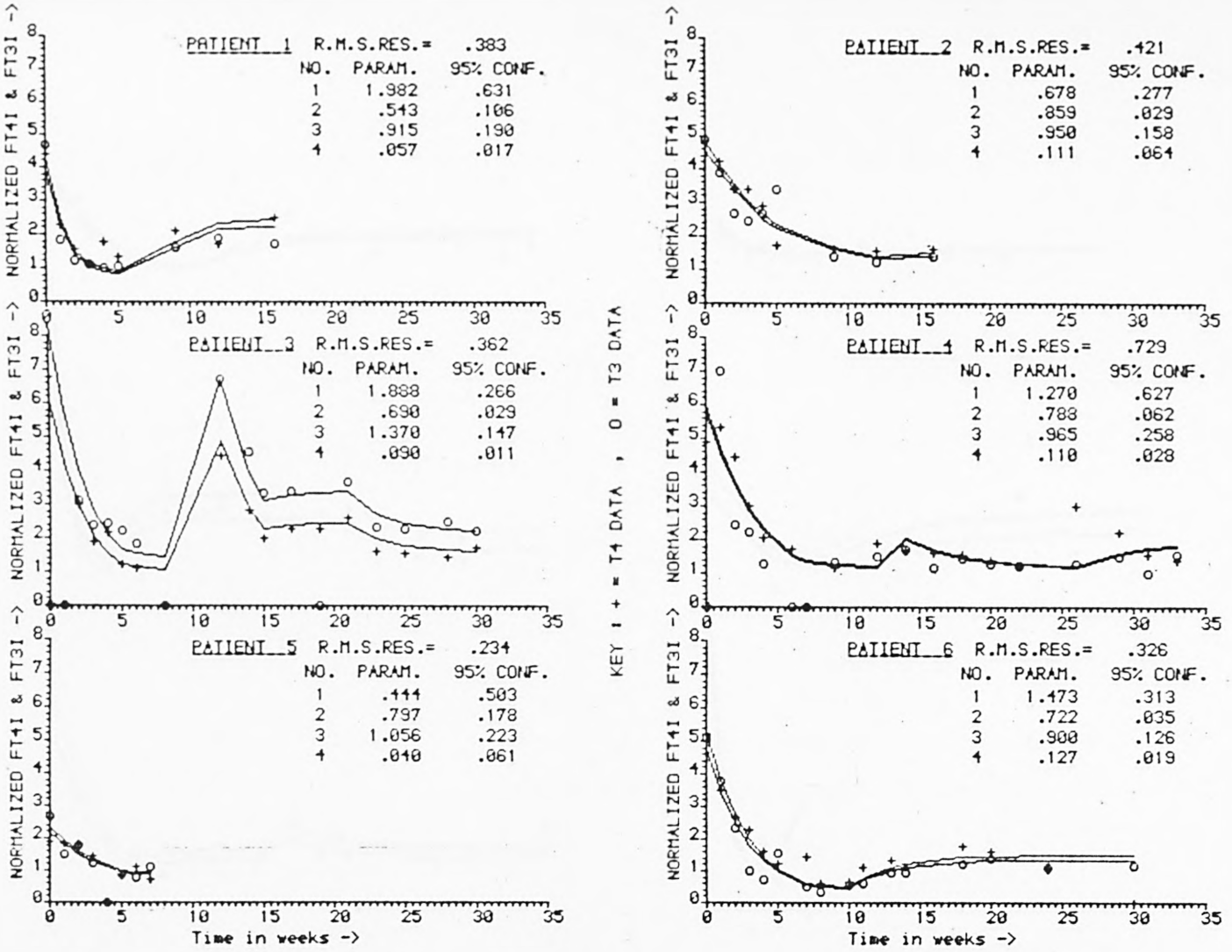
Figure 7.12



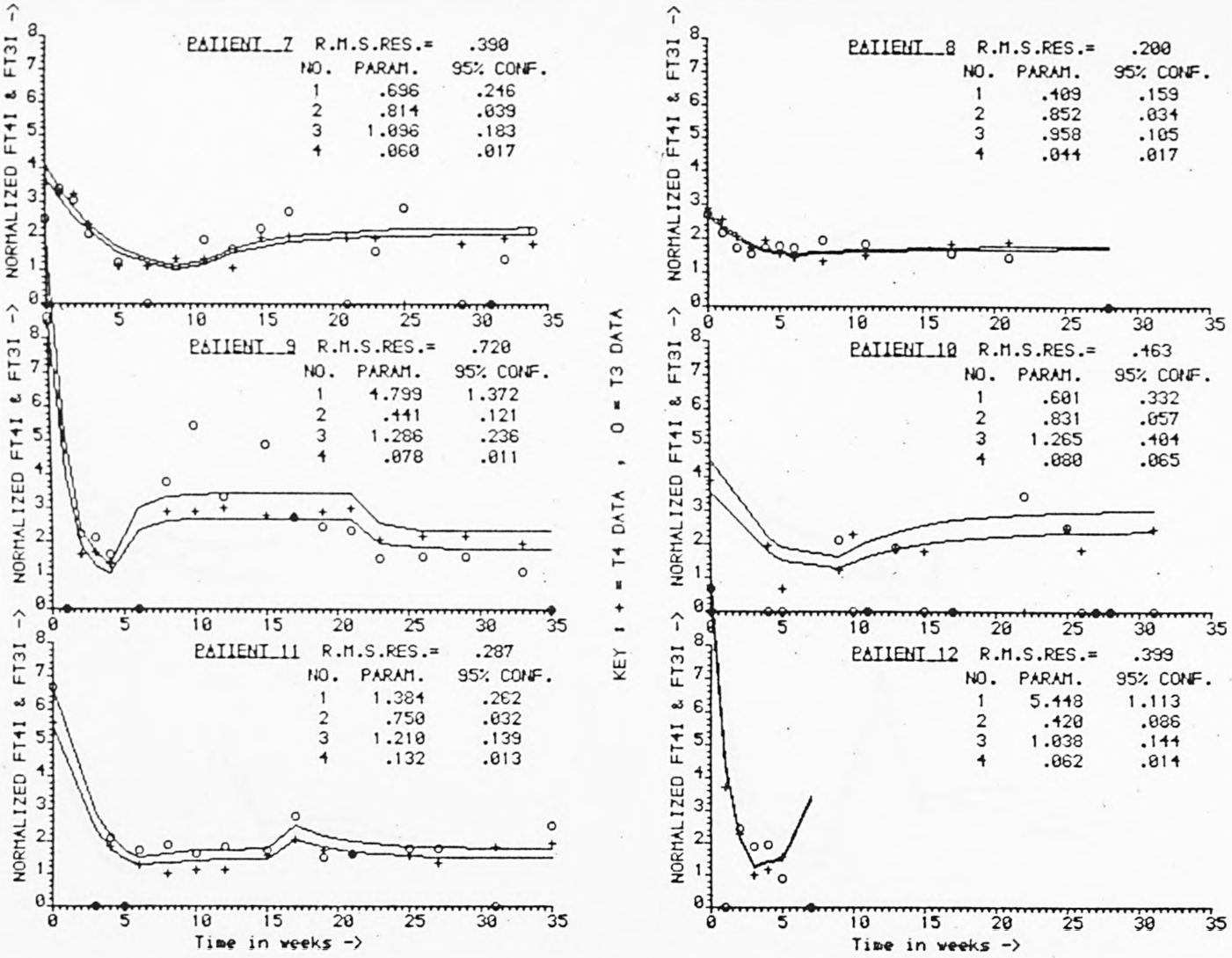
Group fit to reduced thyroidal model excluding an intra-thyroidal compartment Figure 7.13



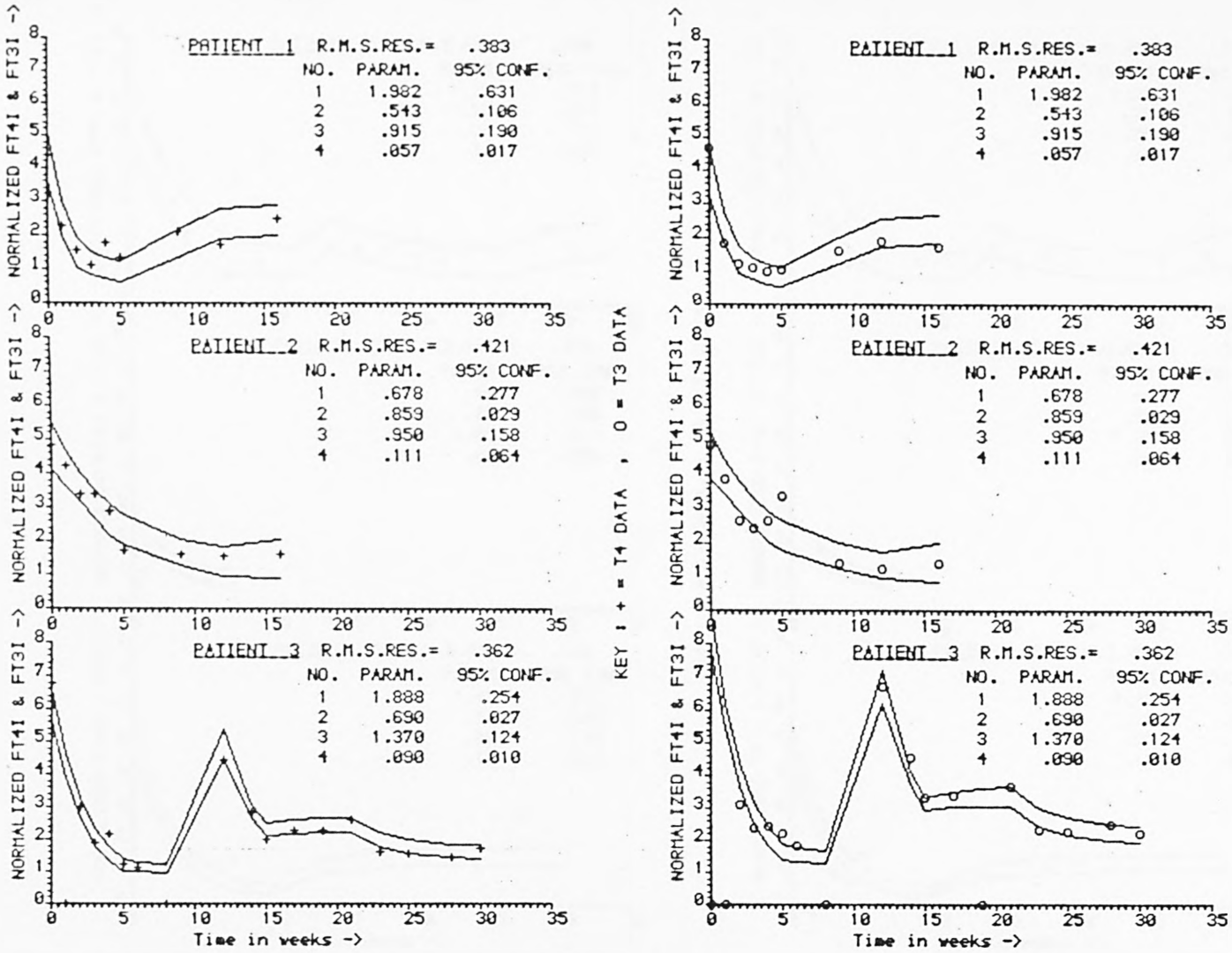
Group fit to reduced thyroidal model excluding an intra-thyroidal compartment Figure 7.14



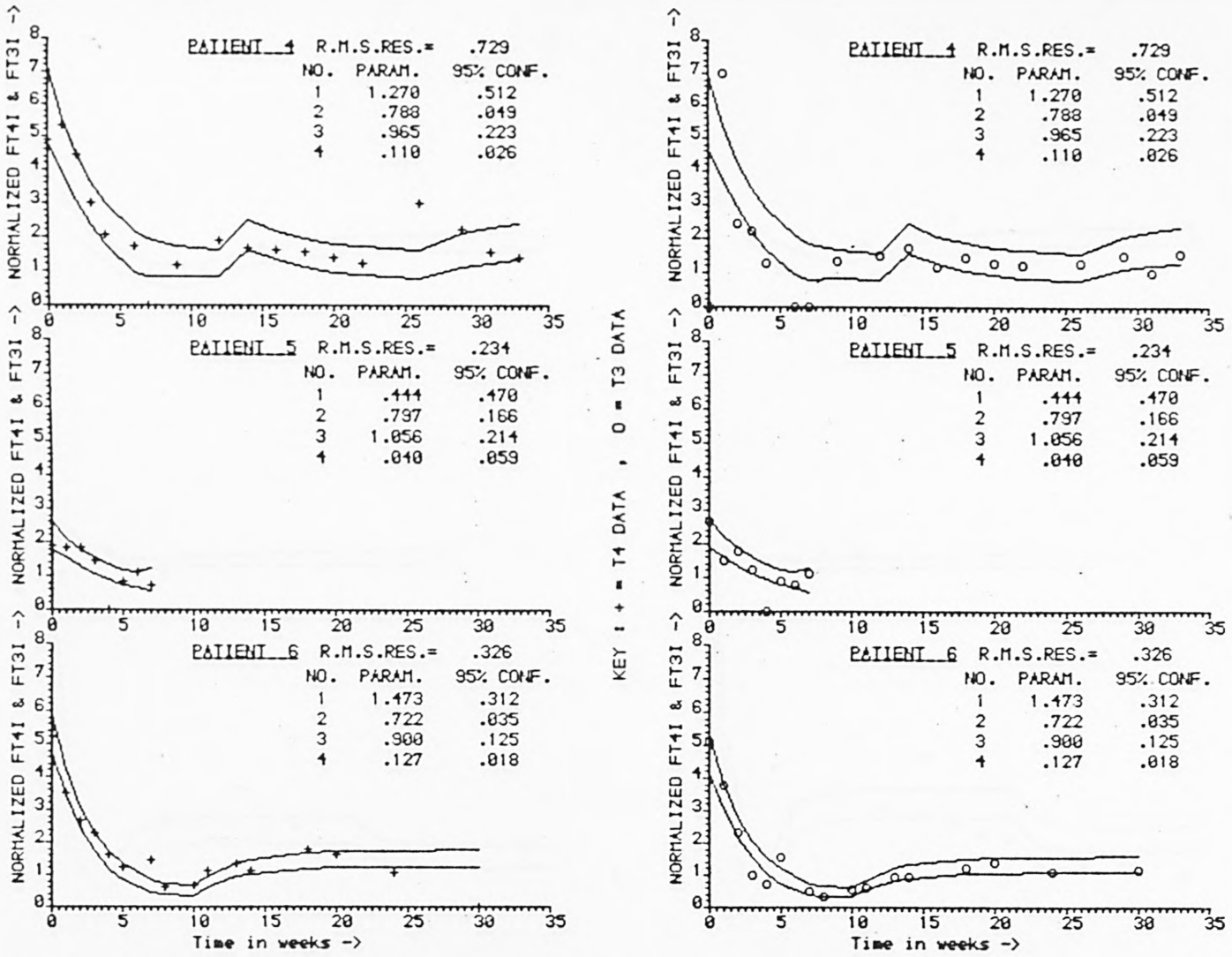
Individual patient data fitted to reduced thyroidal model Figure 7.15



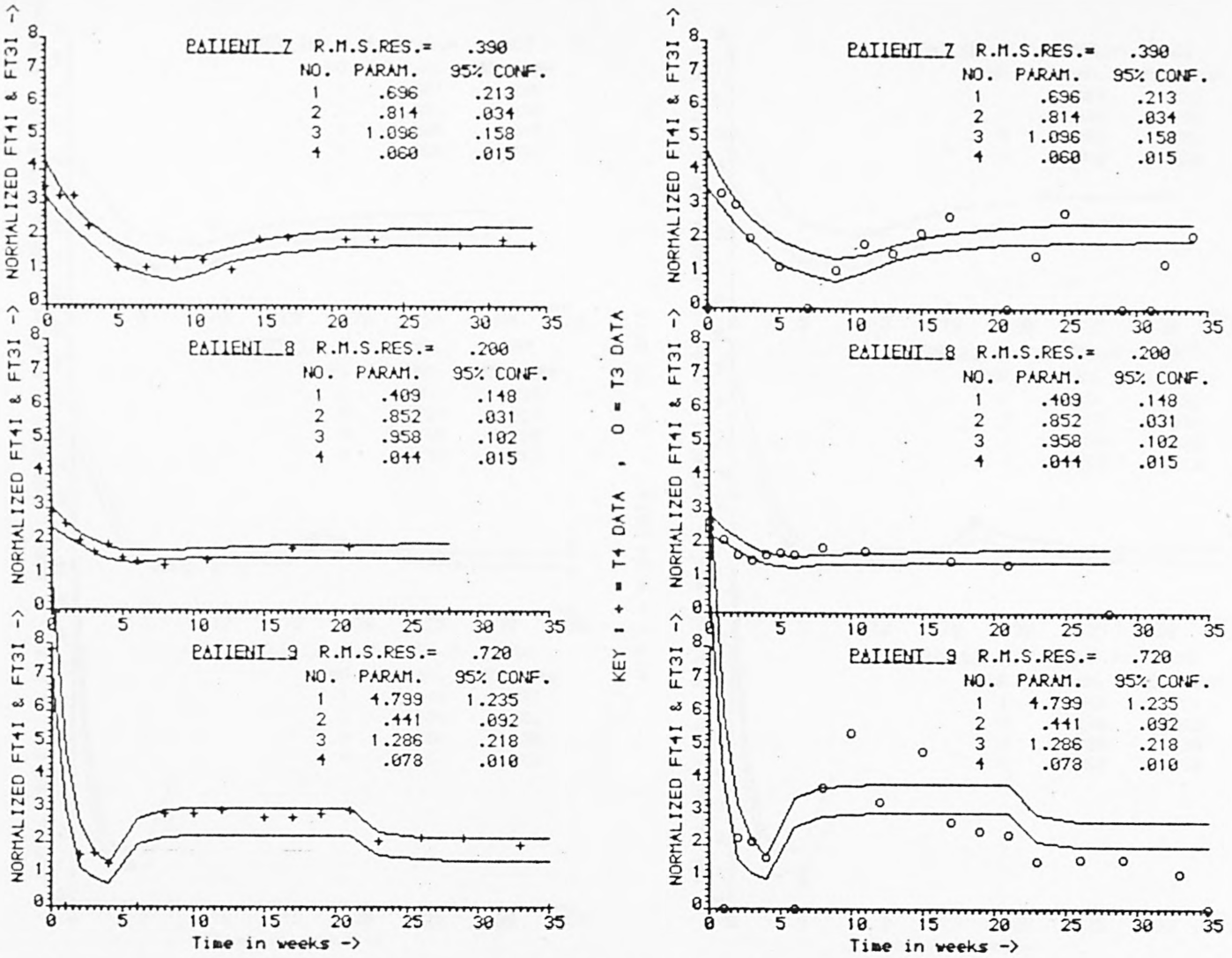
Individual patient data fitted to the reduced thyroidal model Figure 7.16



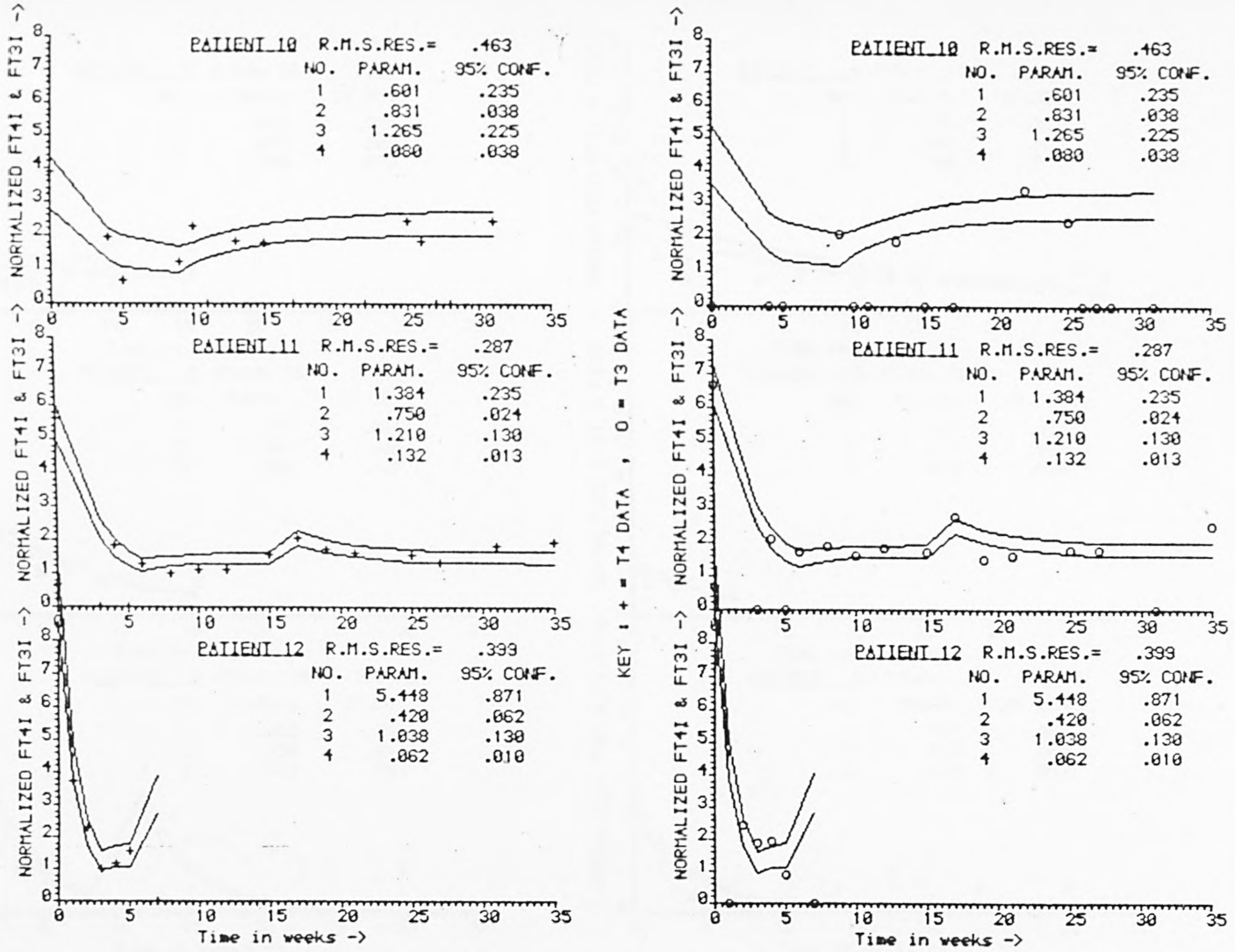
. Confidence limits for model estimates after fitting to each individual patient data Figure 7.17



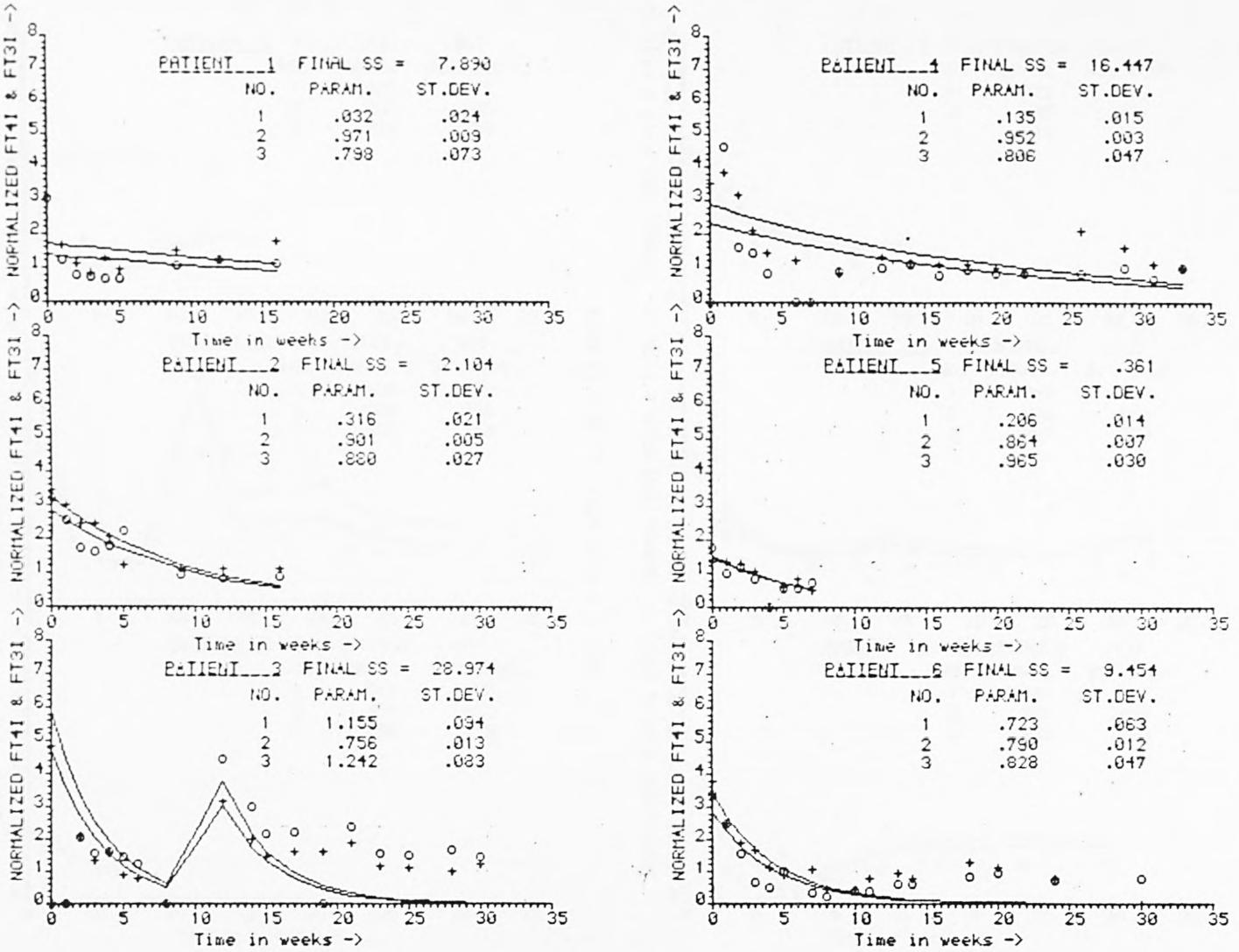
Confidence limits for model estimatesafter fitting to individual patient data Figure 7.18



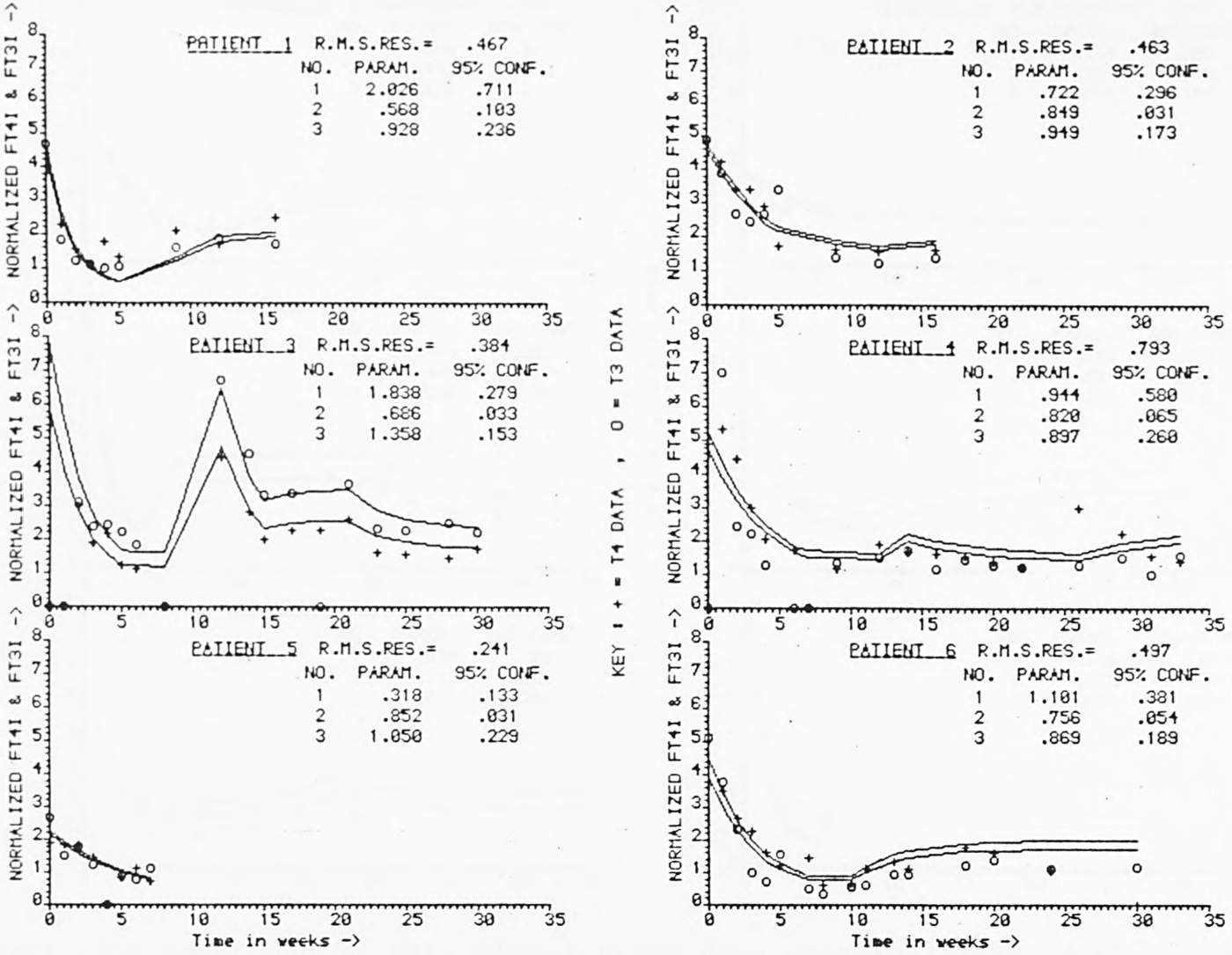
Confidence limits for model estimates after fitting to individual patient data Figure 7.19



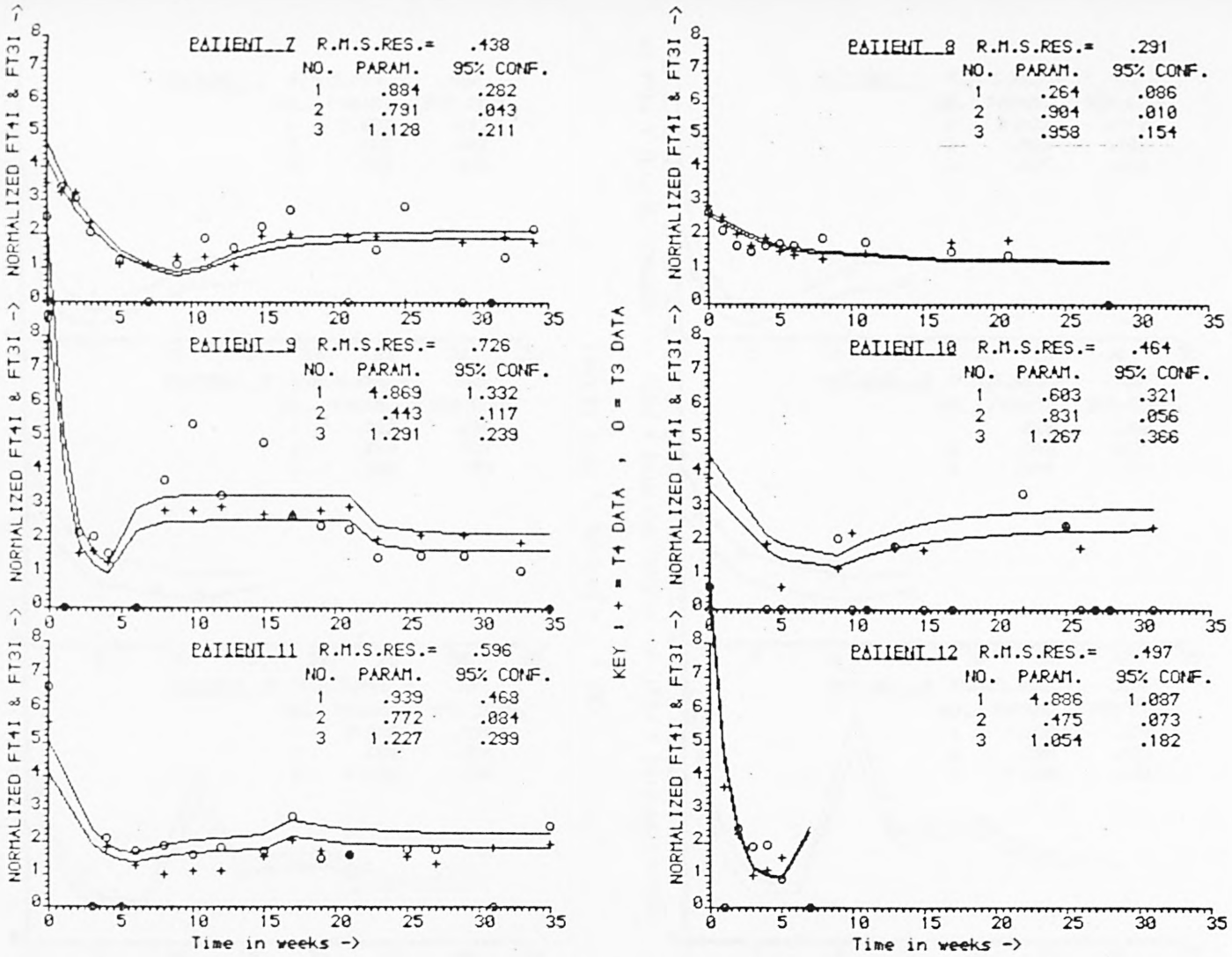
Confidence limits for model estimates after fitting to individual patient data Figure 7.20



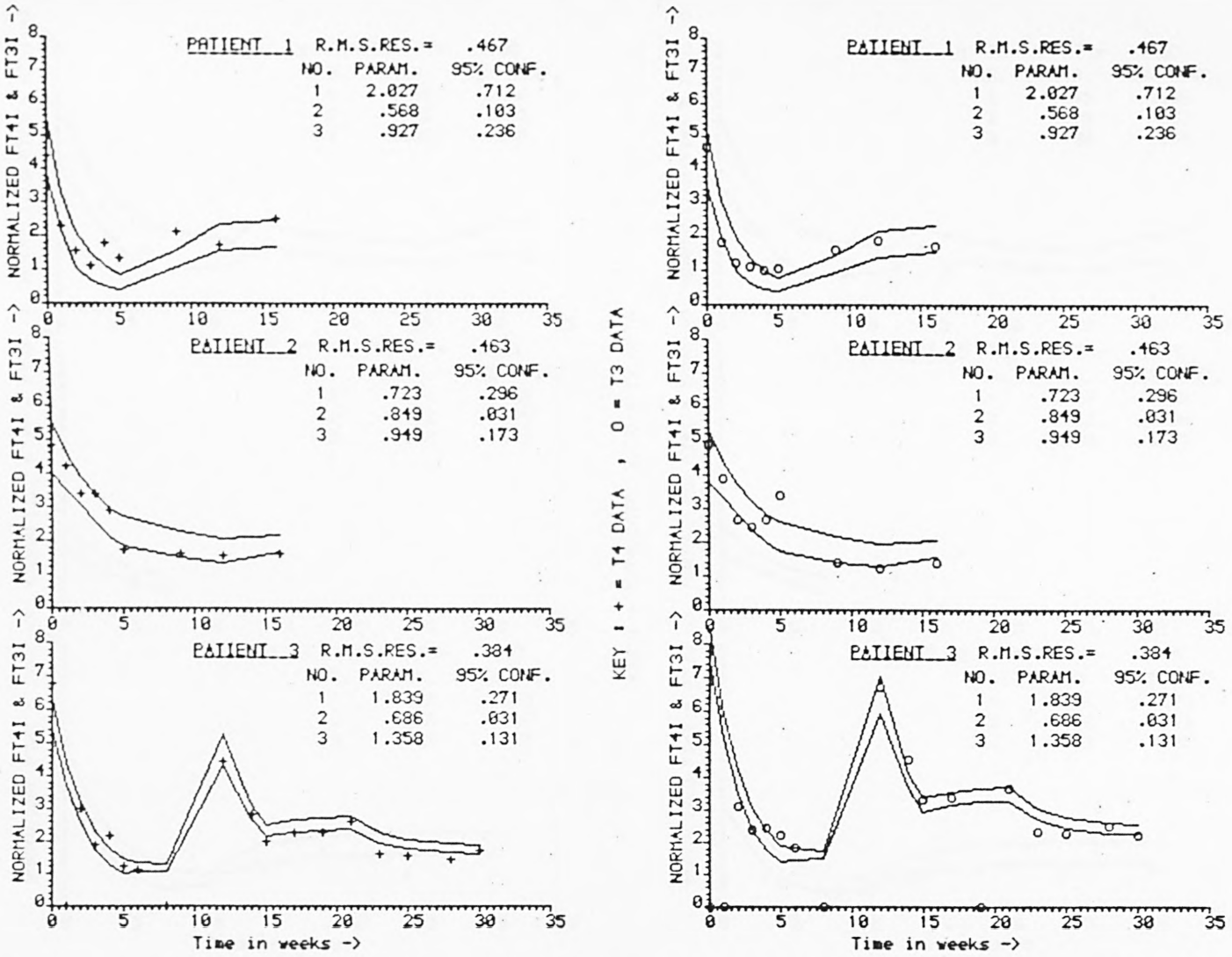
Poor fit obtained for simple linear model of thyroidal response Figure 7.21



Individual fits to T4 and T3 data with a fixed drug sensitivity parameter. Figure 7.22

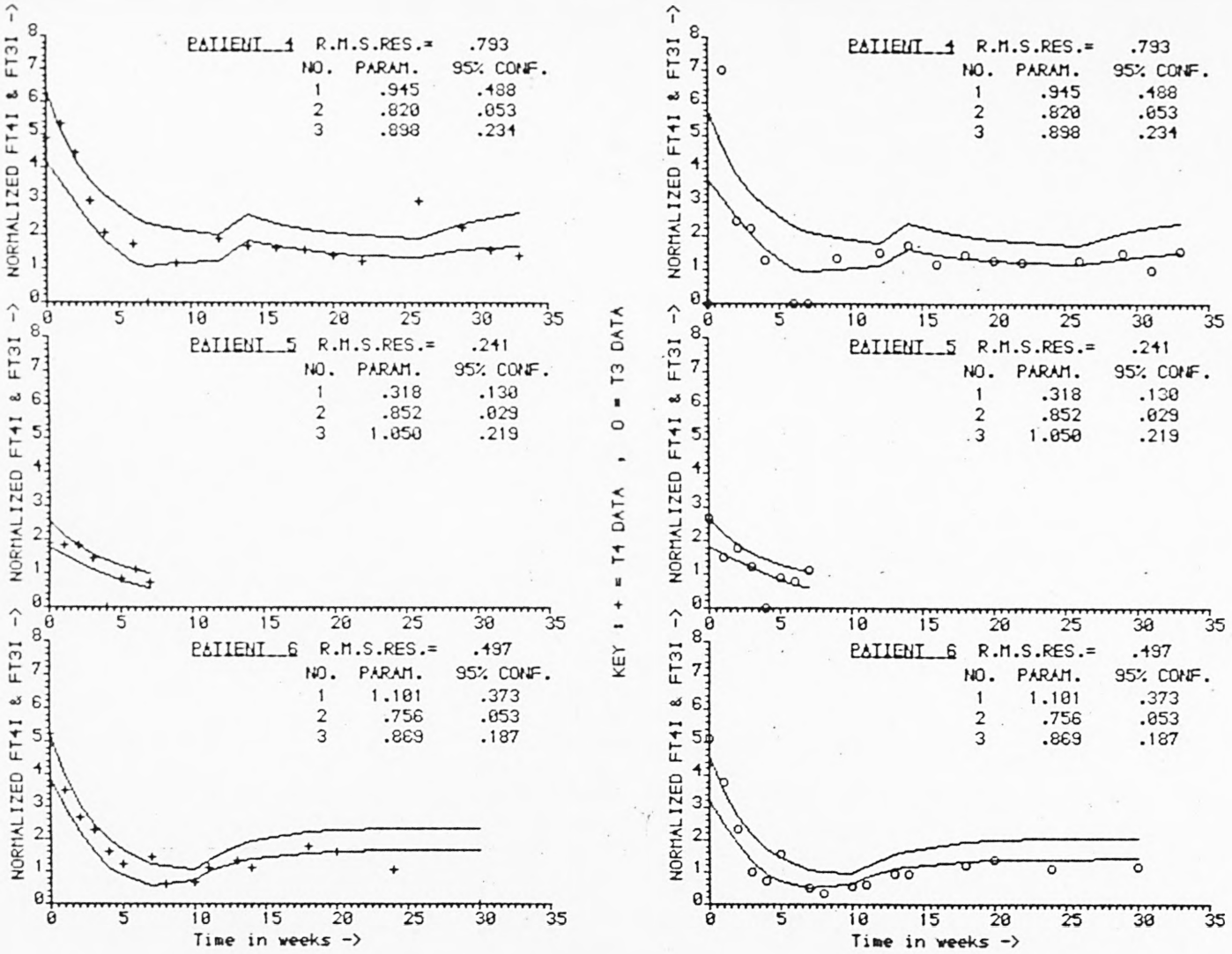


Individual fits to T4 and T3 data with a fixed drug sensitivity paramter Figure 7.23



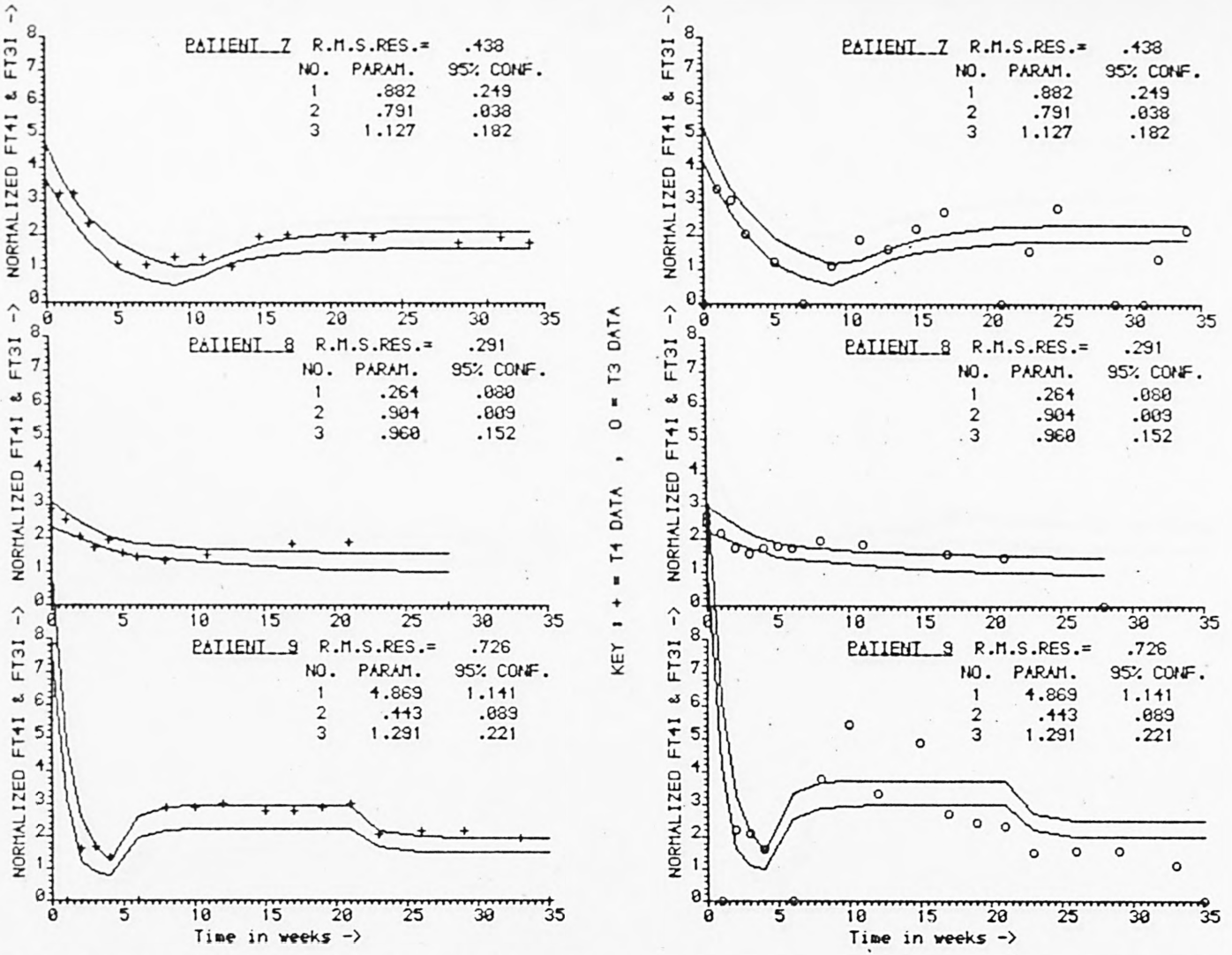
Confidence limits with fixed sensitivity parameter after fitting to individual patient data

Figure 7.24



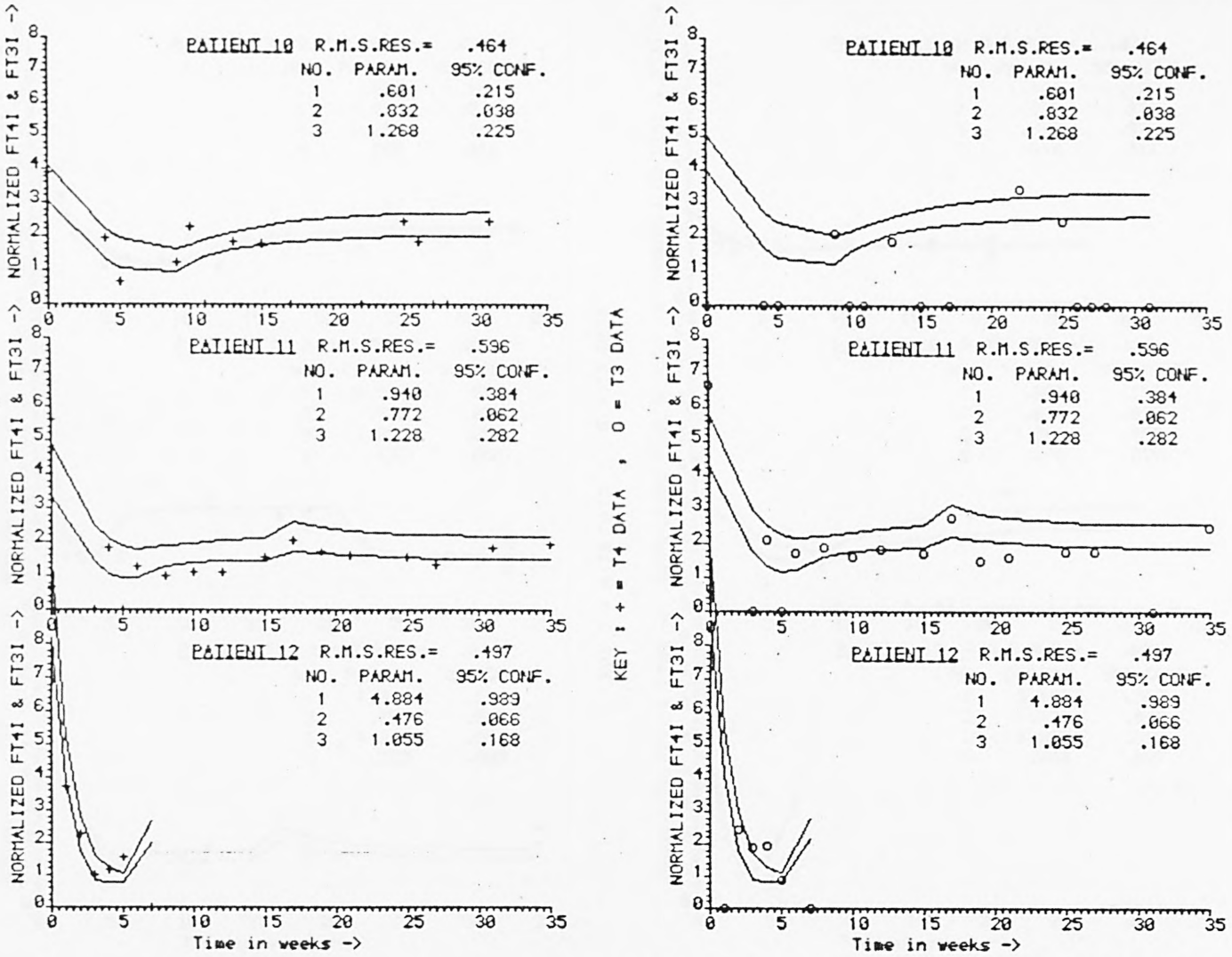
Confidence limits with fixed sensitivity parameter after fitting to individual patient data

Figure 7.25



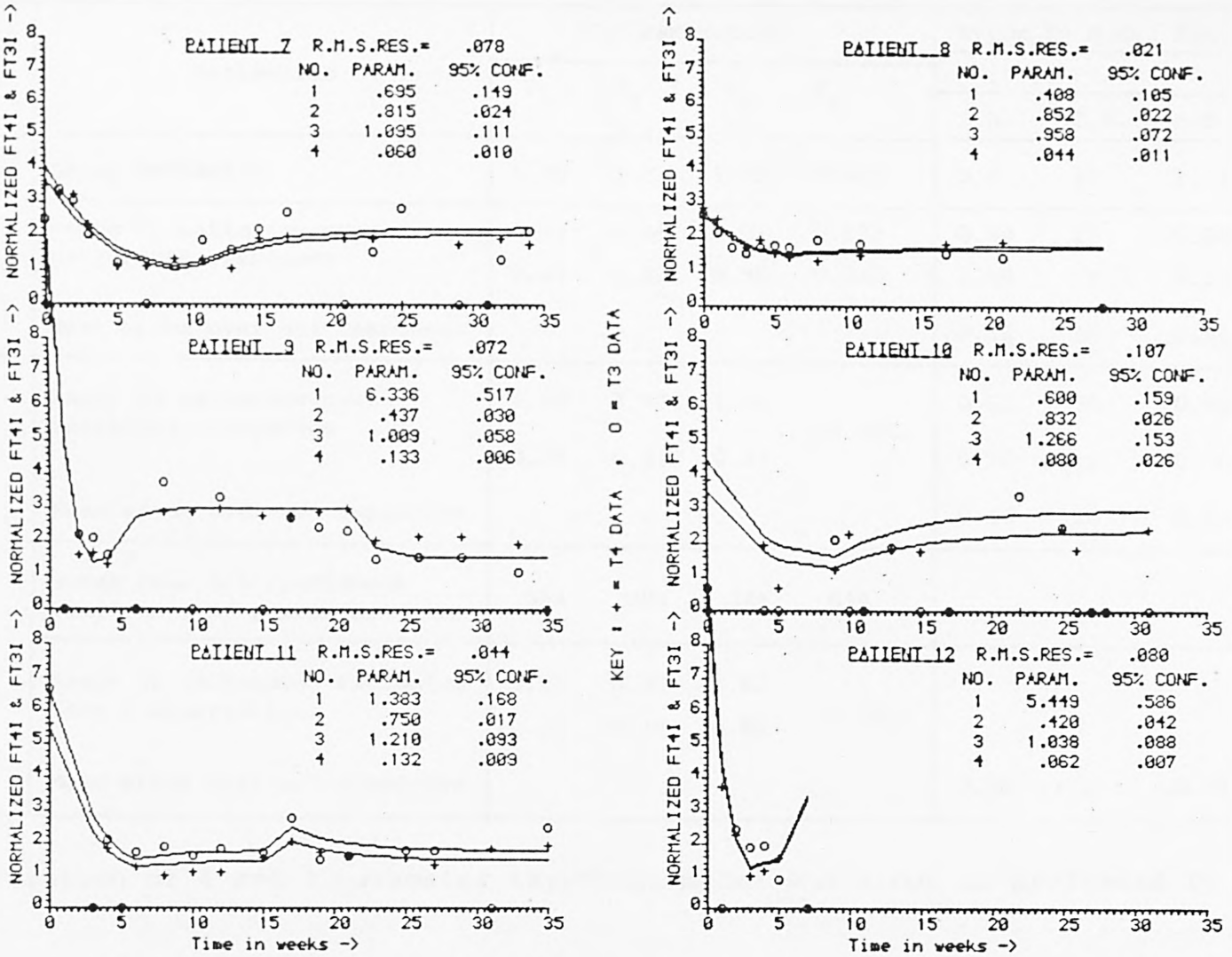
Confidence limits with fixed sensitivity parameter after fitting to individual patient data

Figure 7.26



Confidence limits with fixed sensitivity parameter after fitting to individual patient data

Figure 7. 27



Re-estimation of parameters of model for patient 9 after removal of 'outlier'T3 results

Figure 7.28

No. of parameters	Estimation	Parameters				Error in Model Fitting			
						T4		T3	
		P_1	P_2	P_3	P_4	S.D.	%C.V.	S.D.	%C.V.
4	Group estimates	1.30	0.73	1.09	0.081	0.91	41	1.22	54
	Range of estimates over individual responses	5.44	0.86	1.37	0.132	0.64	27	0.98	45
		0.41	0.42	0.90	0.040	0.18	9	0.23	13
	Mean error over all responses					0.36	16	0.54	24
3	Range of estimates over individual responses	4.89	0.904	1.36	(0.081)	0.62	30	0.97	52
		0.26	0.443	0.87		0.20	12	0.30	13
	Mean error over all responses					0.43	20	0.62	27
	Worst case 95% confidence limit as % of parameter value	55%	27%	32%	81%				
	Range of individual estimates from 5 observations	5.06	0.87	1.82	(0.081)				
		0.32	0.45	0.89					
	Mean error over all responses					0.56	25	0.81	36

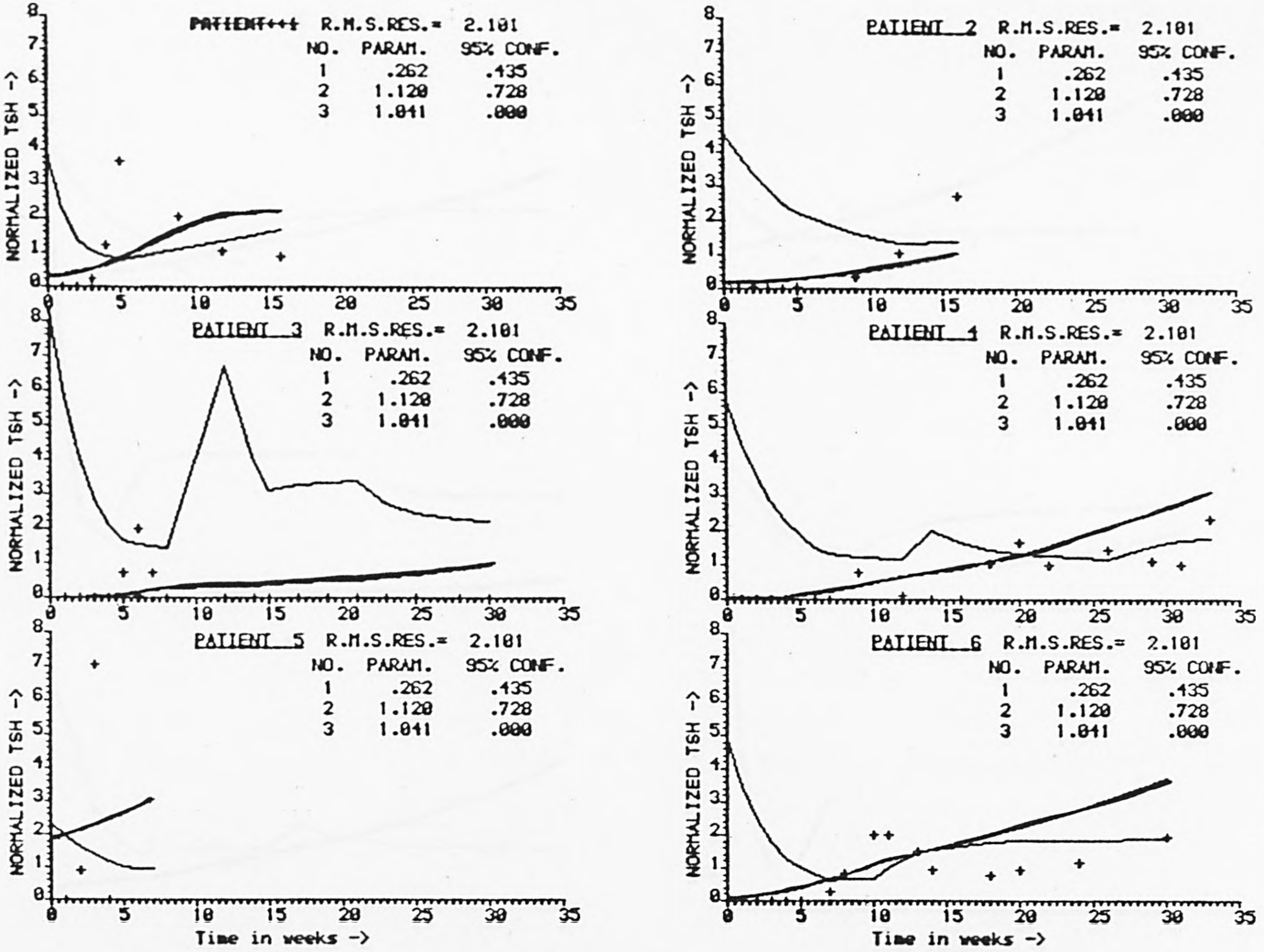
Identification of 4 and 3 parameter thyroidal model and error in predicted T4 and T3 data

Figure 7.29

+ - Normalised TSH measures

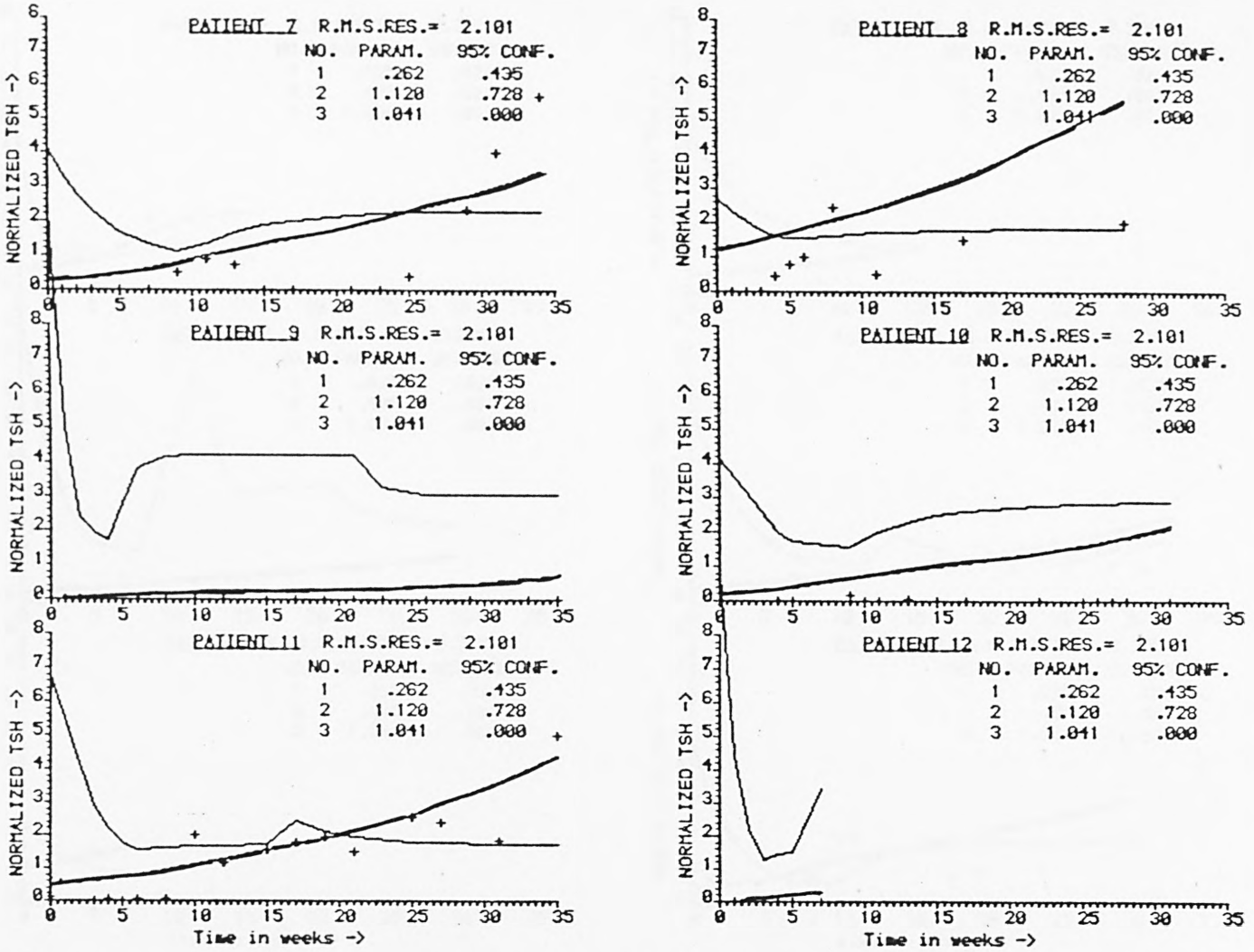
Heavy line - response of pituitary model

Fine line - driving T3 response for this patient



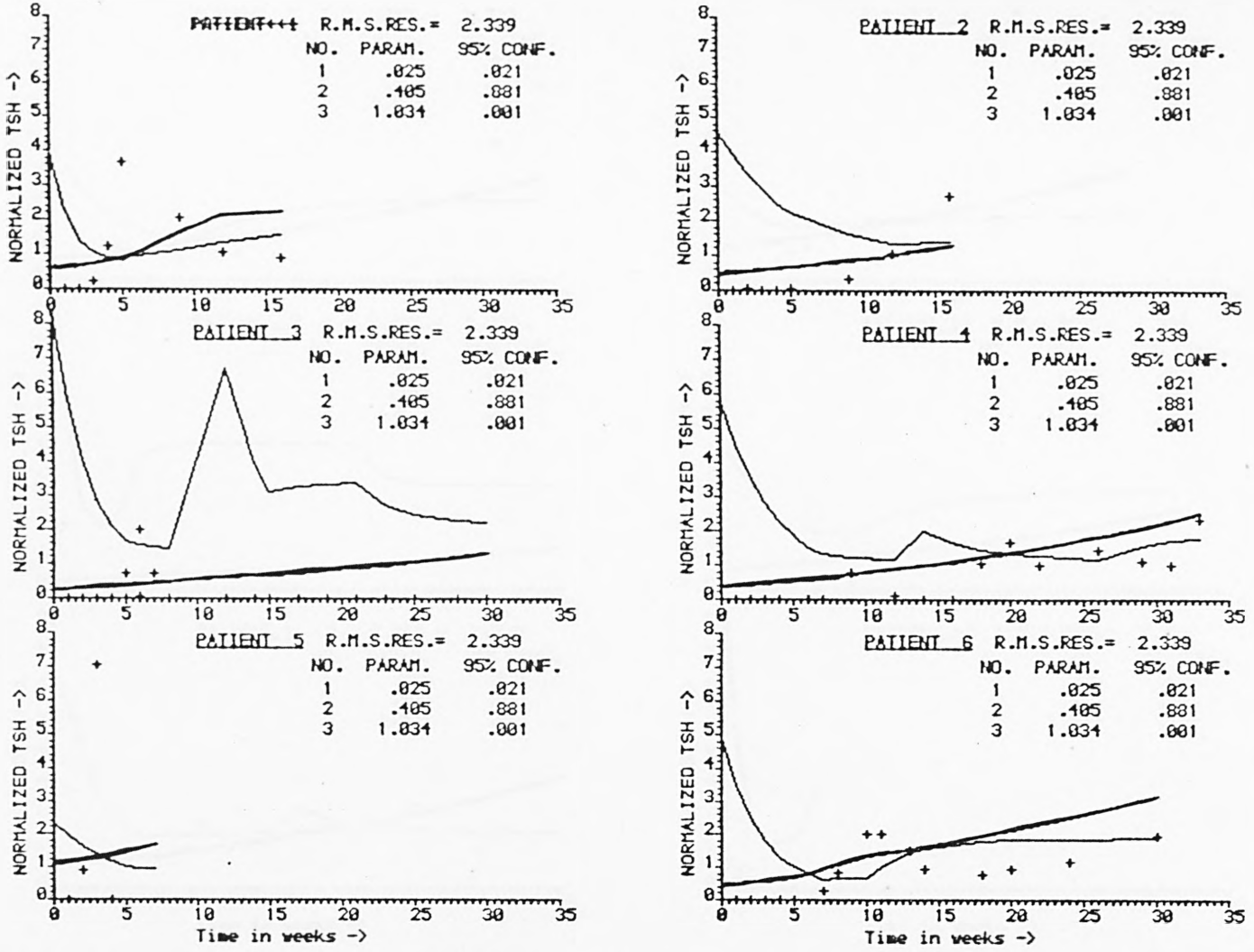
Group fit of exponential model of pituitary reponse following the response of the thyroidal subsystem to carbimazole

Figure 7.30



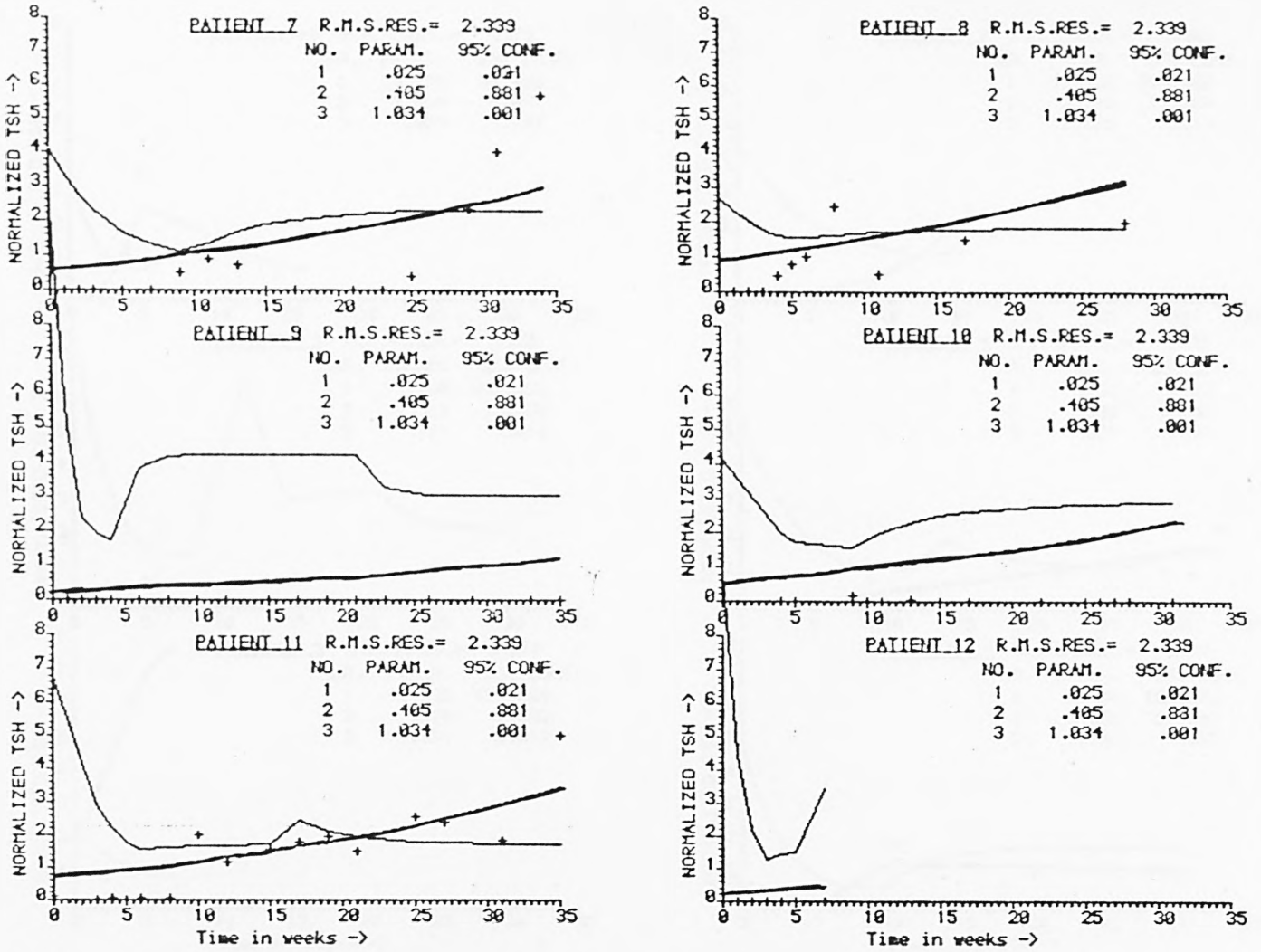
Group fit of exponential model of pituitary response

Figure 7.31



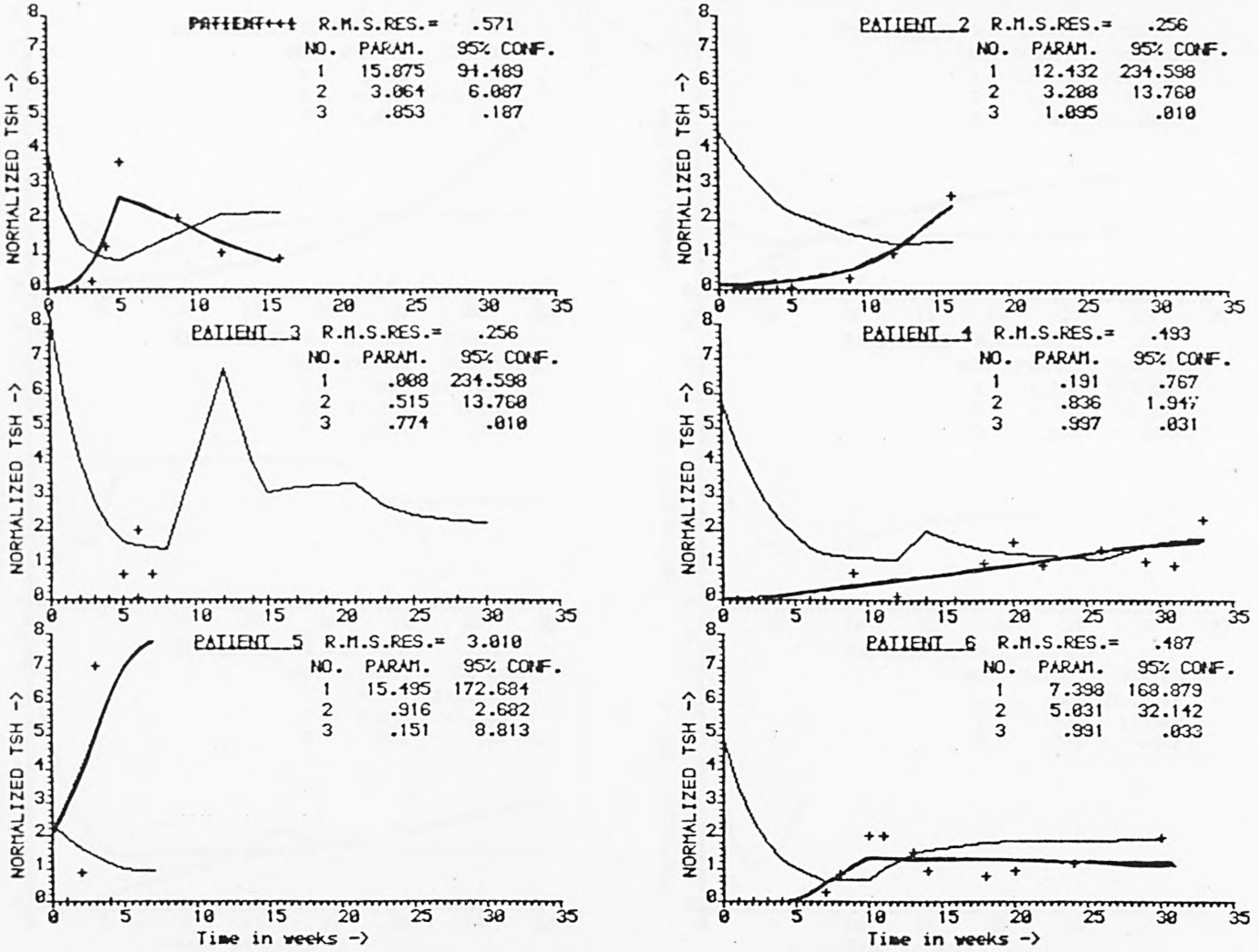
Group fit of reciprocal model of pituitary response

Figure 7.32

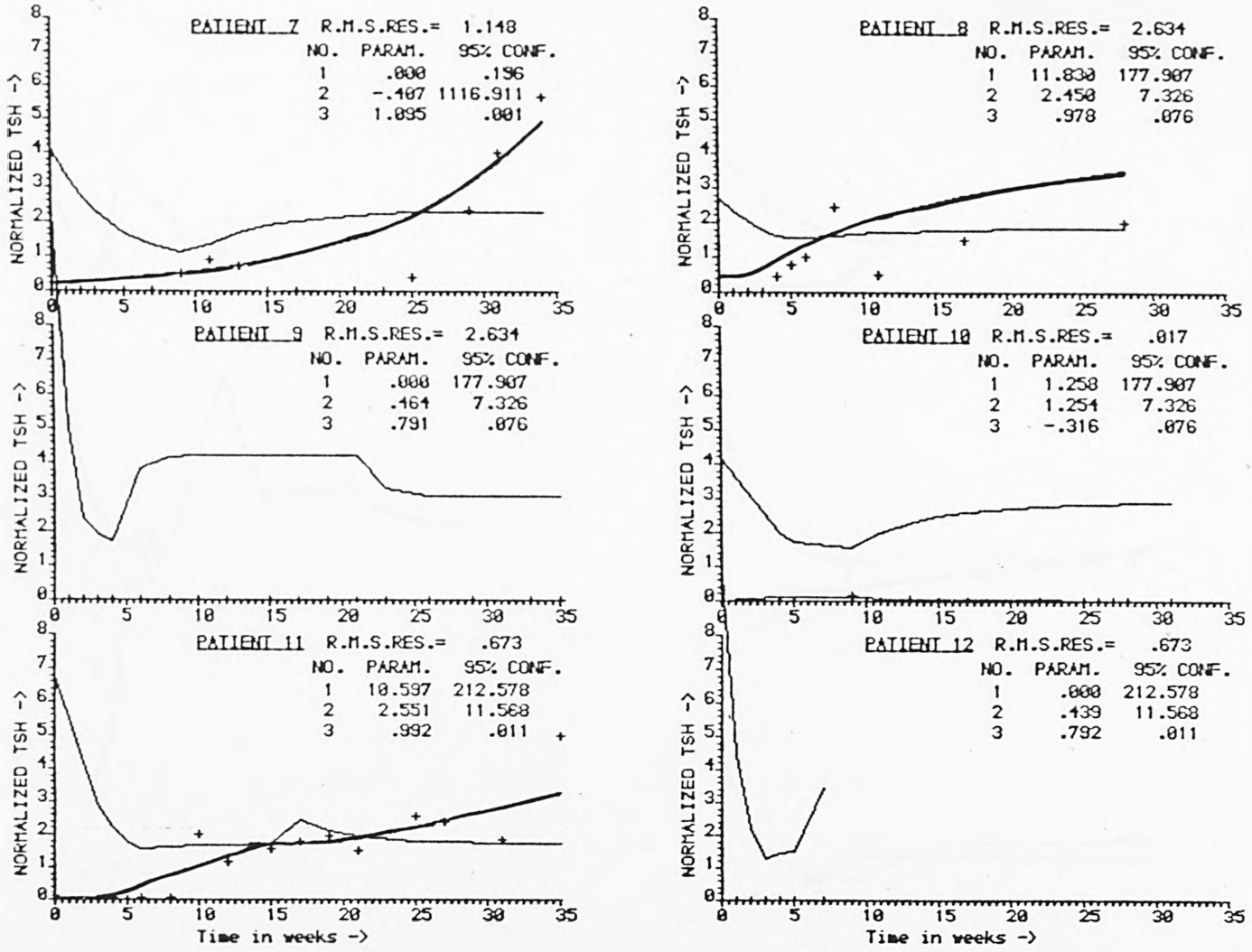


Group fit of reciprrocal model of pituitary response

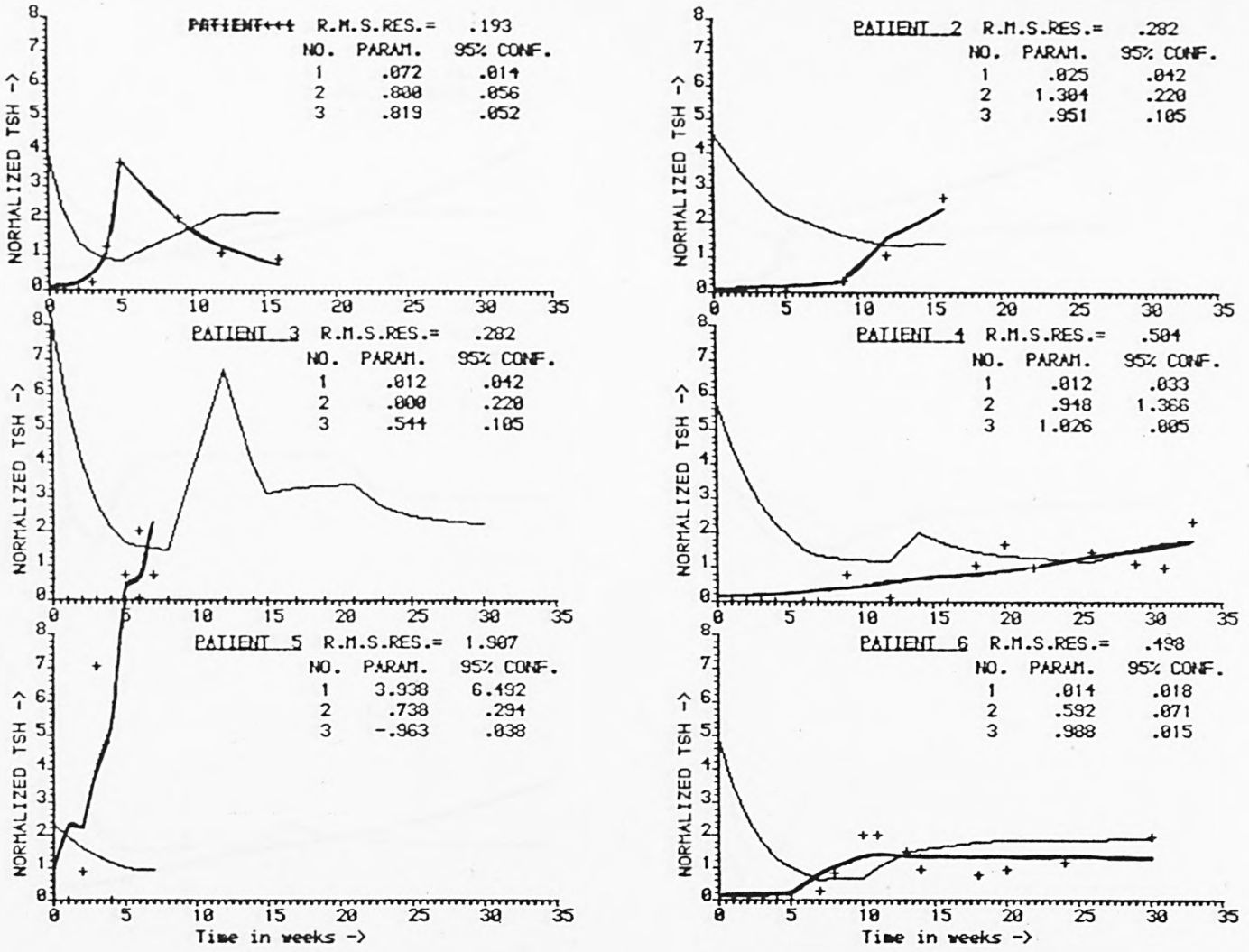
Figure 7.33



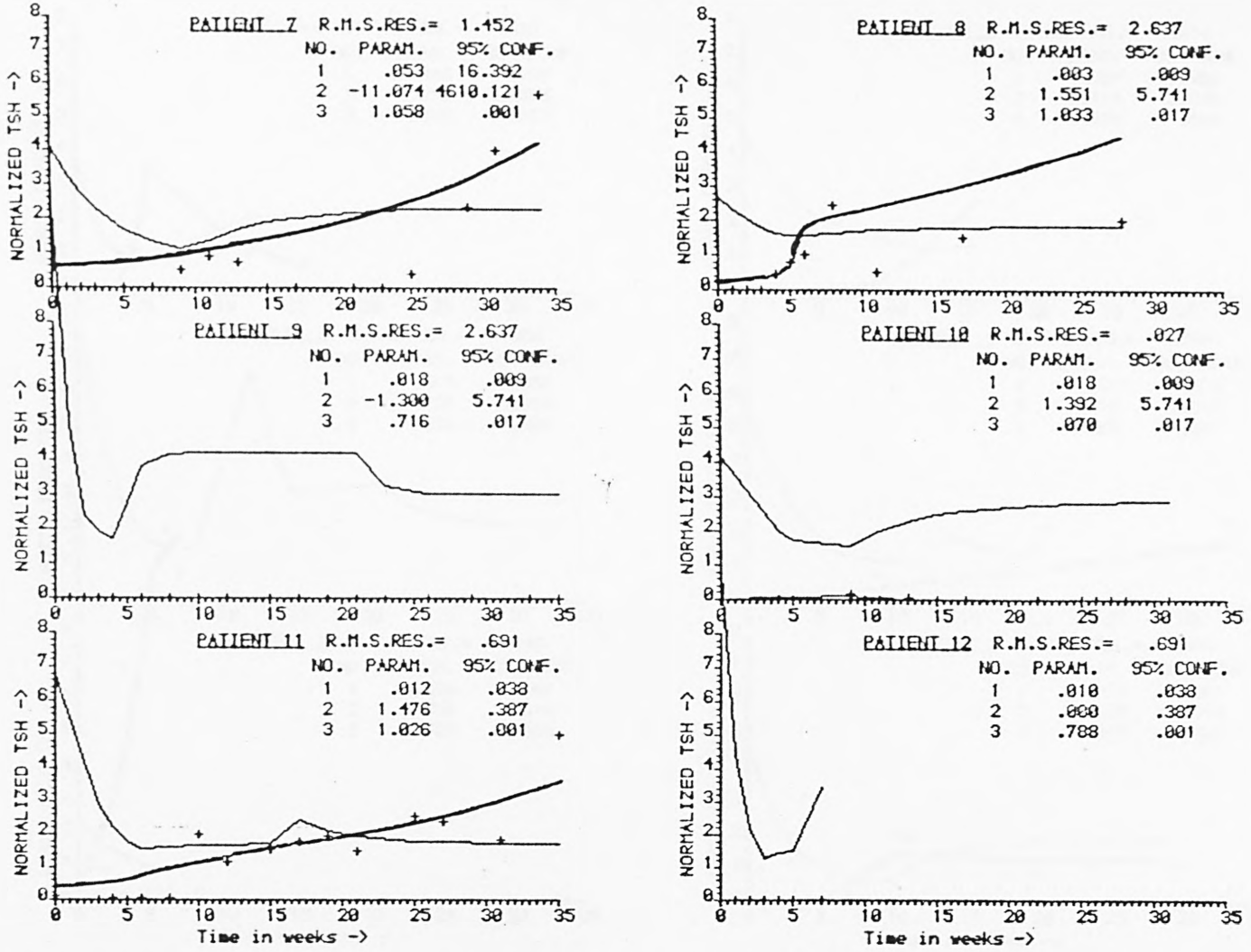
Individual fits obtained for exponential model of pituitary response Figure 7.34



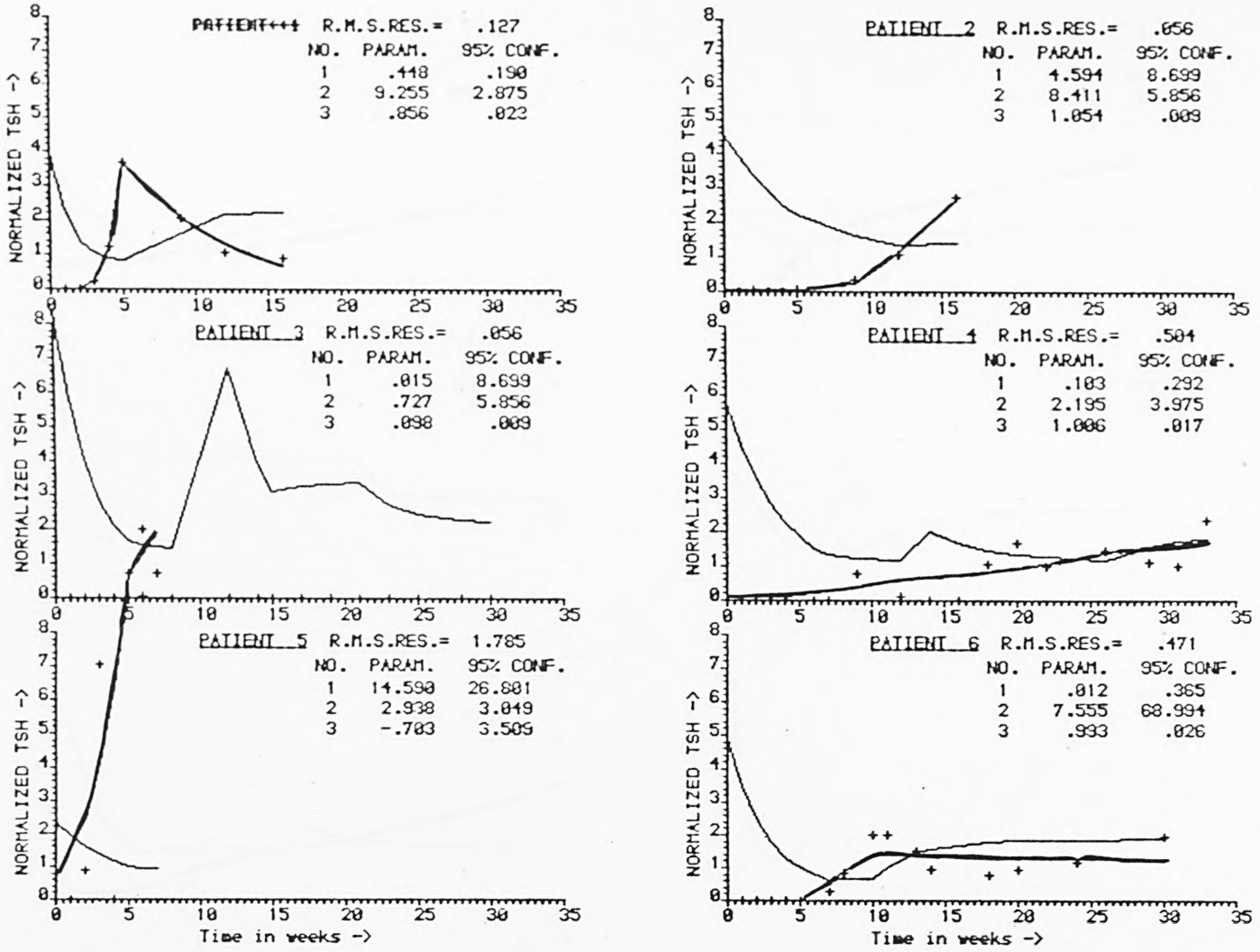
Individual fits obtained with the exponential model of pituitary response Figure 7.35



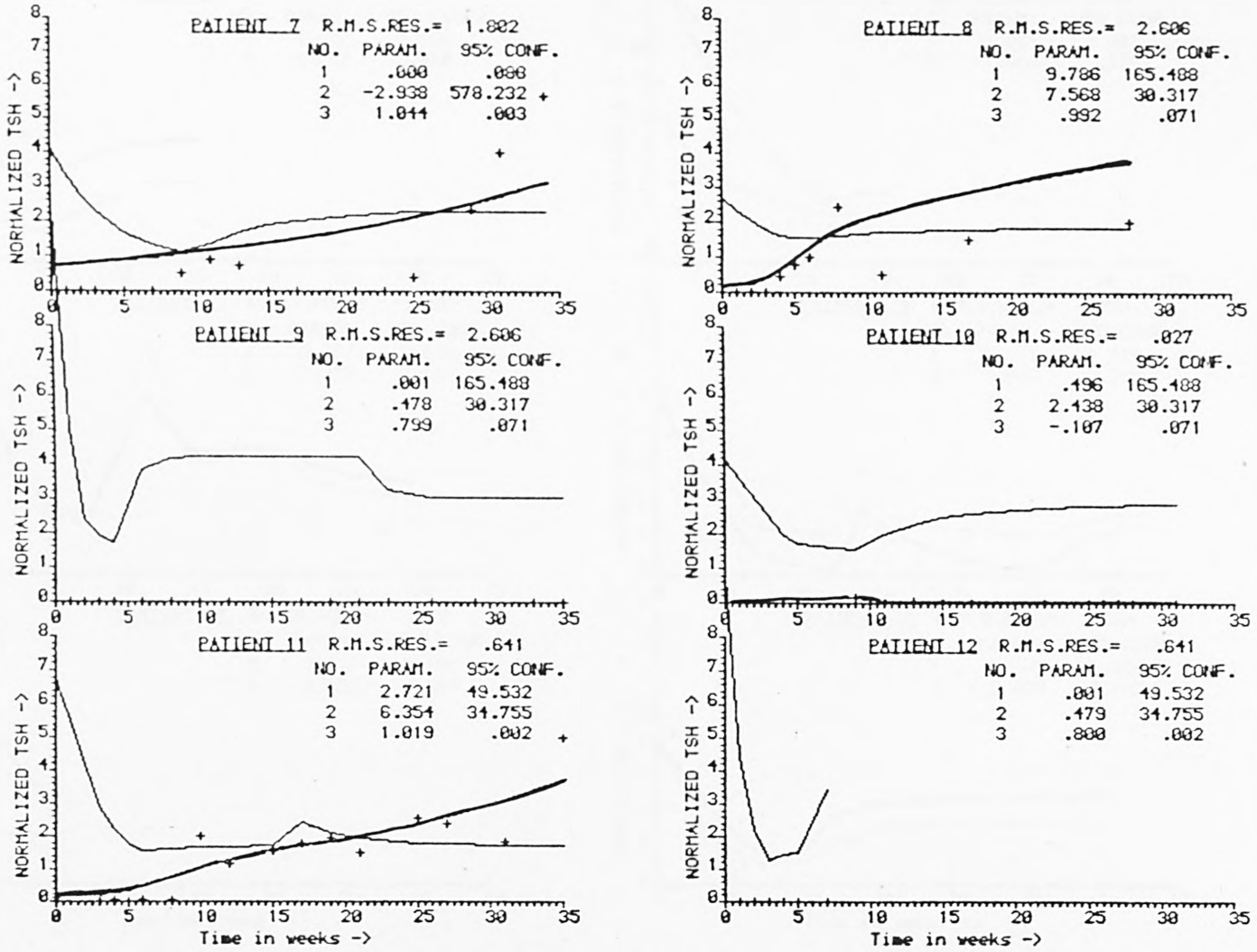
Individual fits obtained with the reciprocal model of pituitary response Figure 7.36



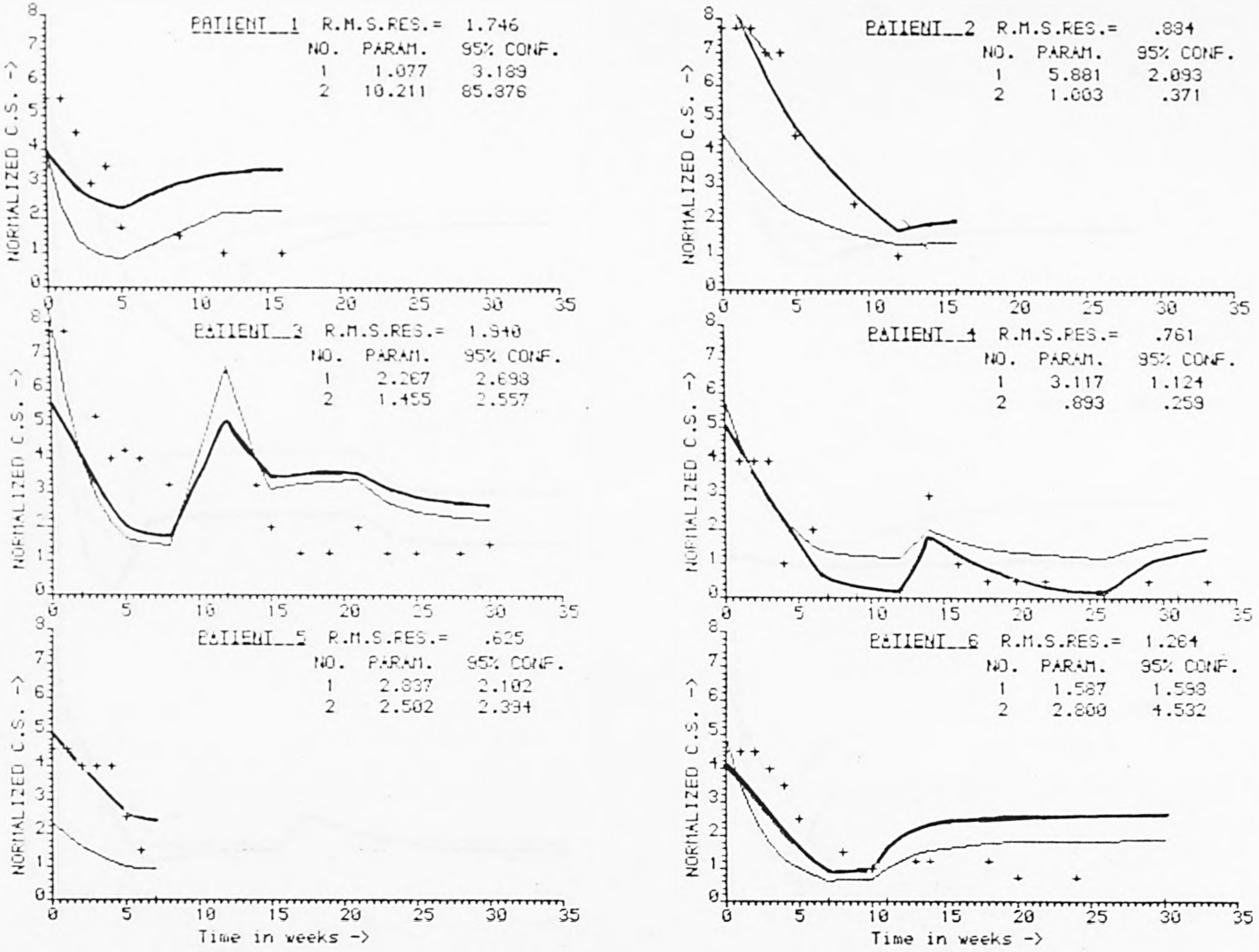
Individual responses obtained with the reciprocal model of pituitary response Figure 7.37



Individual fits obtained with a reciprocal power model of pituitary response Figure 7.38

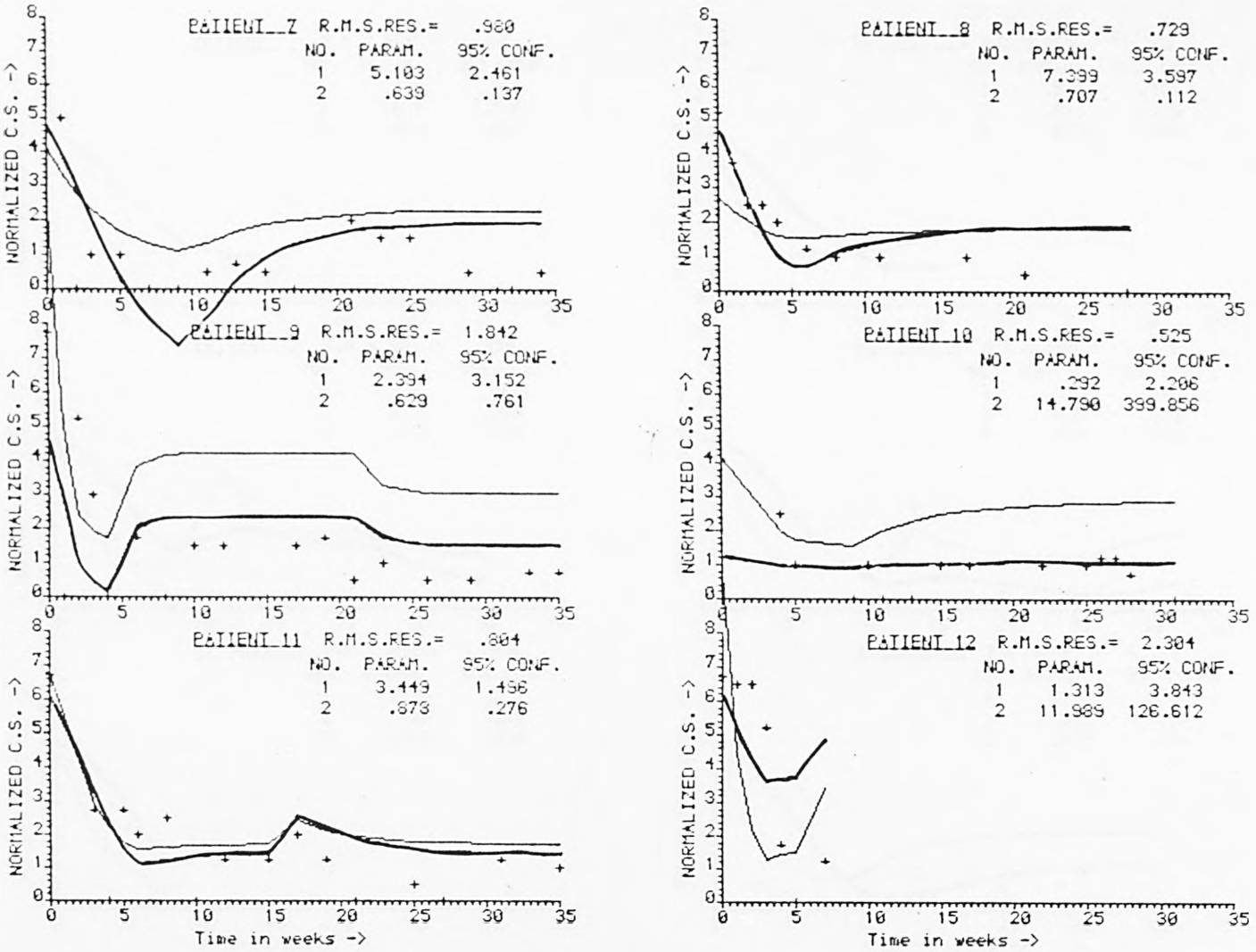


Individual fits obtained with a reciprocal power model of pituitary response Figure 7.39

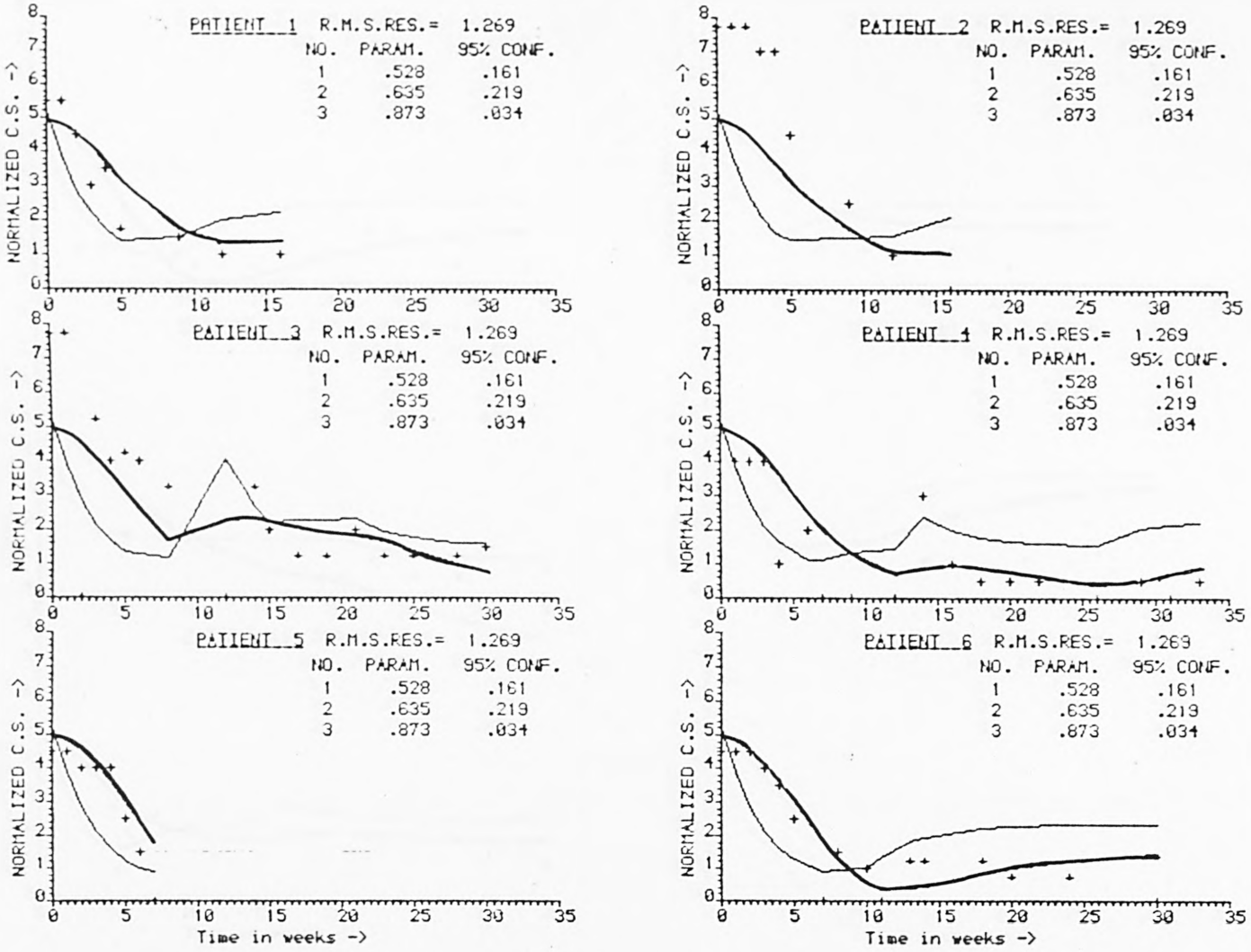


Clinical state shown by +
Clinical response of model shown by thick line
Input to model (T3 response) shown by thin line

Individual fits of a simple exponential model of clinical response Figure 7.40

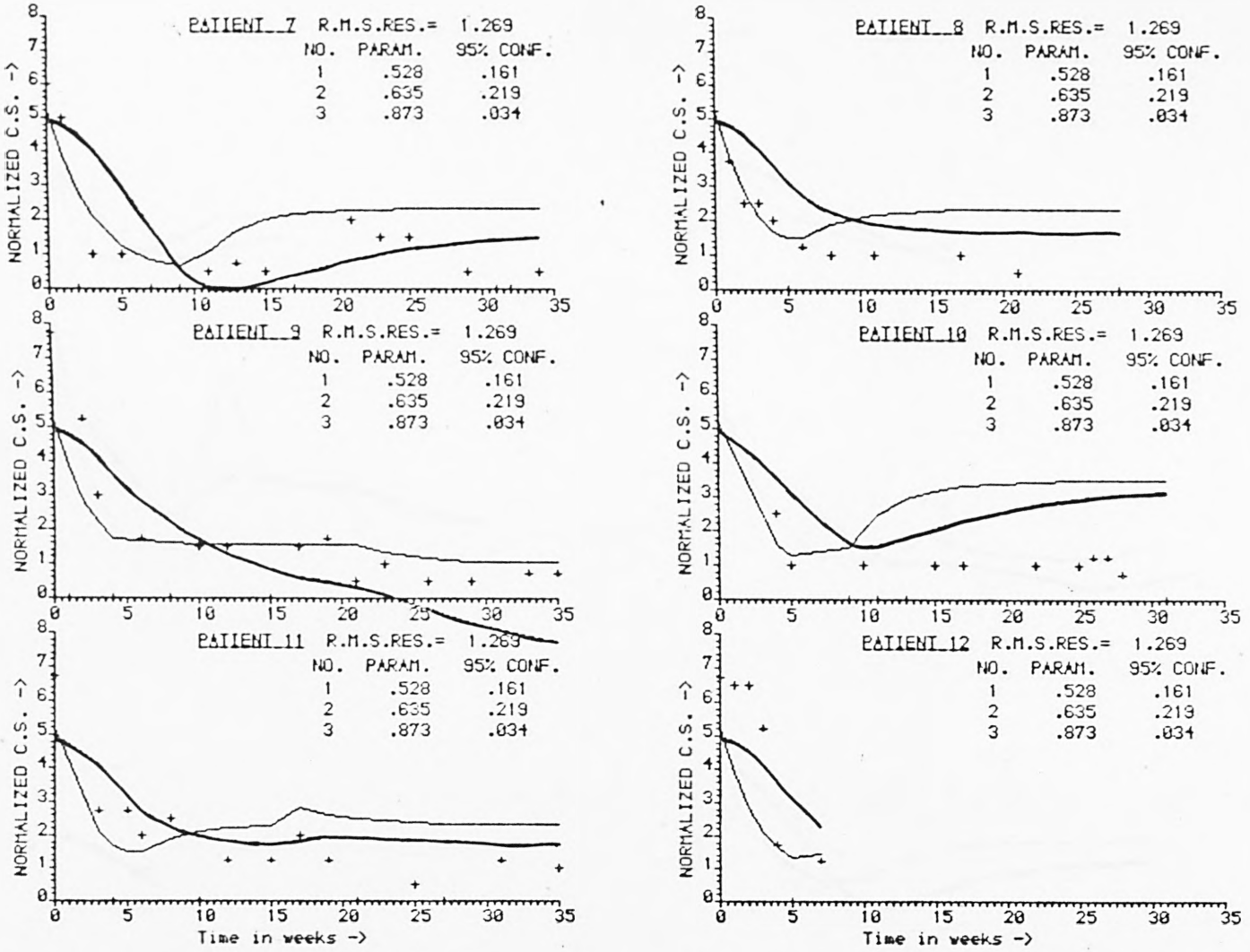


Individual fits of a simple exponential model of clinical response Figure 7.41



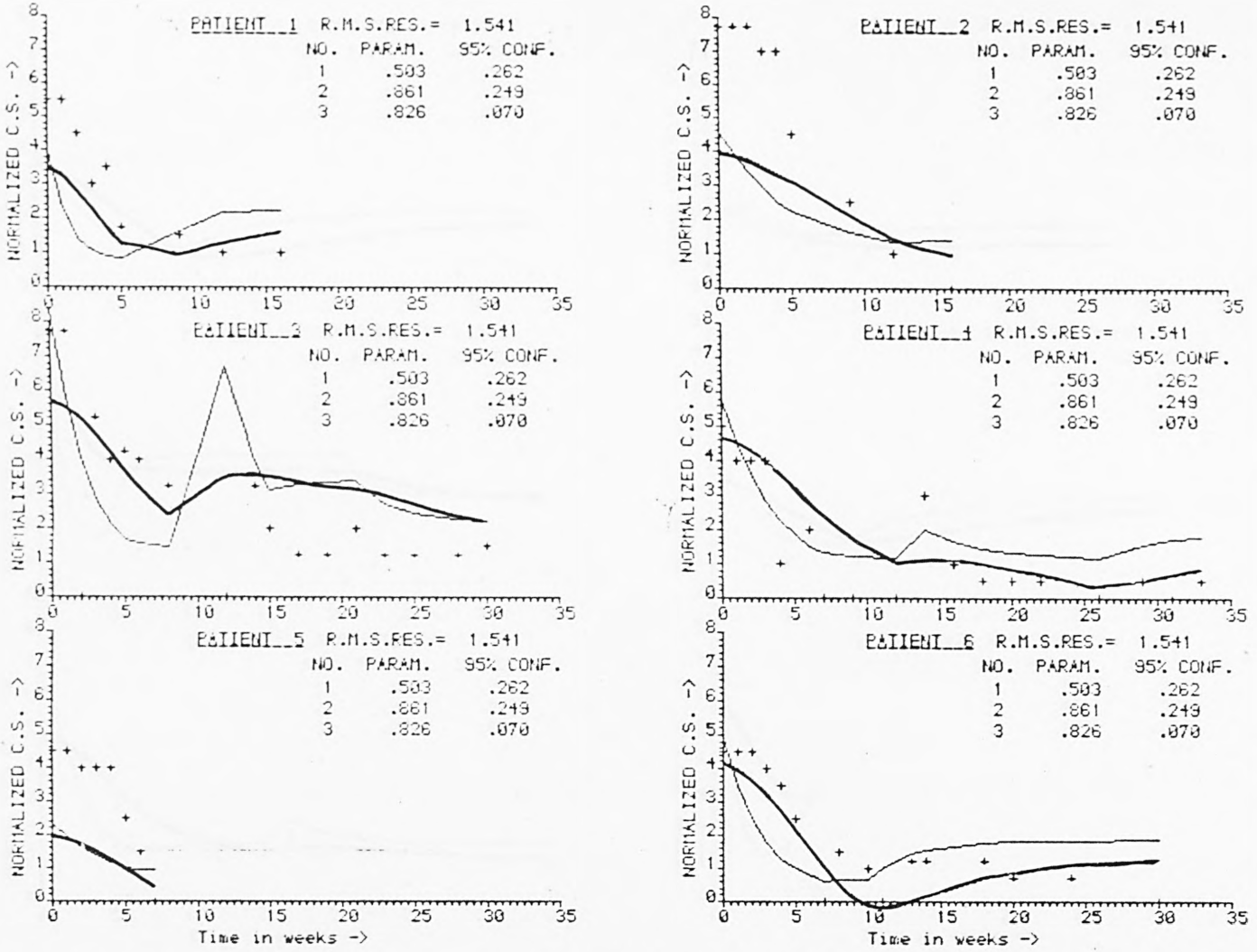
Group fit of model of clinical state including a lag term driven by a "typical" T3 response

Figure 7.42



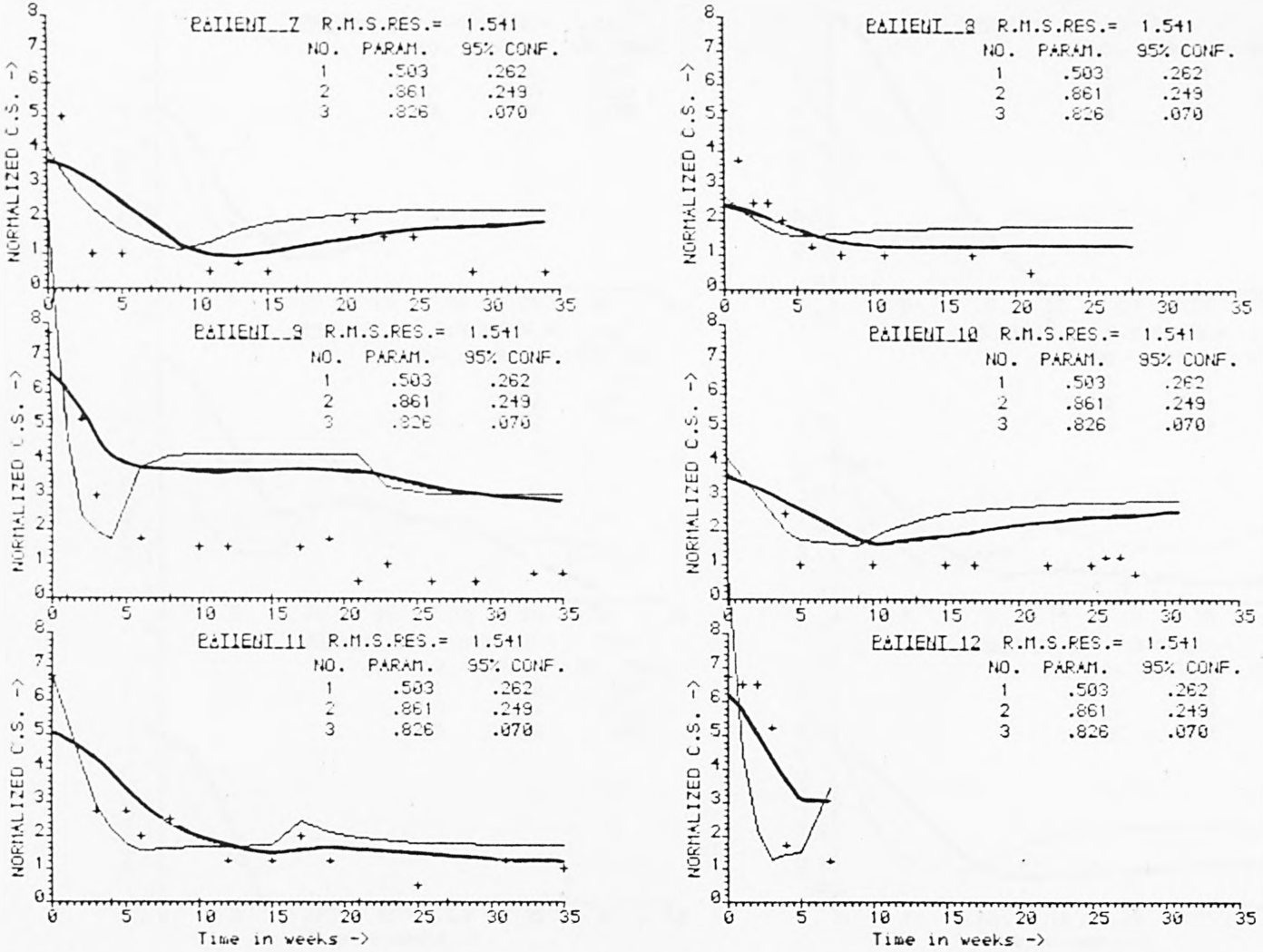
Group fit of model of clinical state including a lag term driven by a "typical" T3 response

Figure 7.43



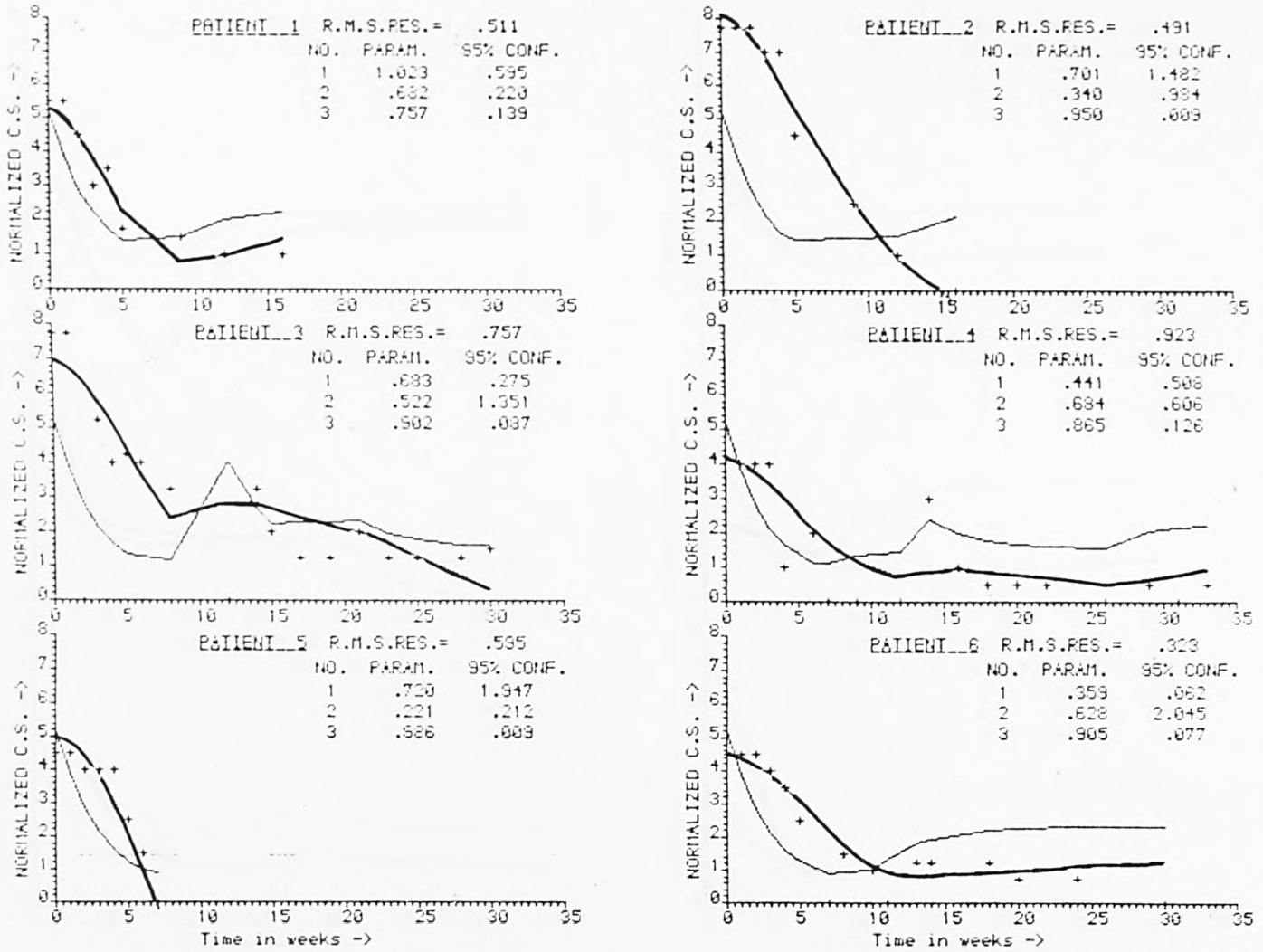
Group fit of model of clinical state including a lag term driven by individually optimised T3 responses (see figure 7.15)

Figure 7.44



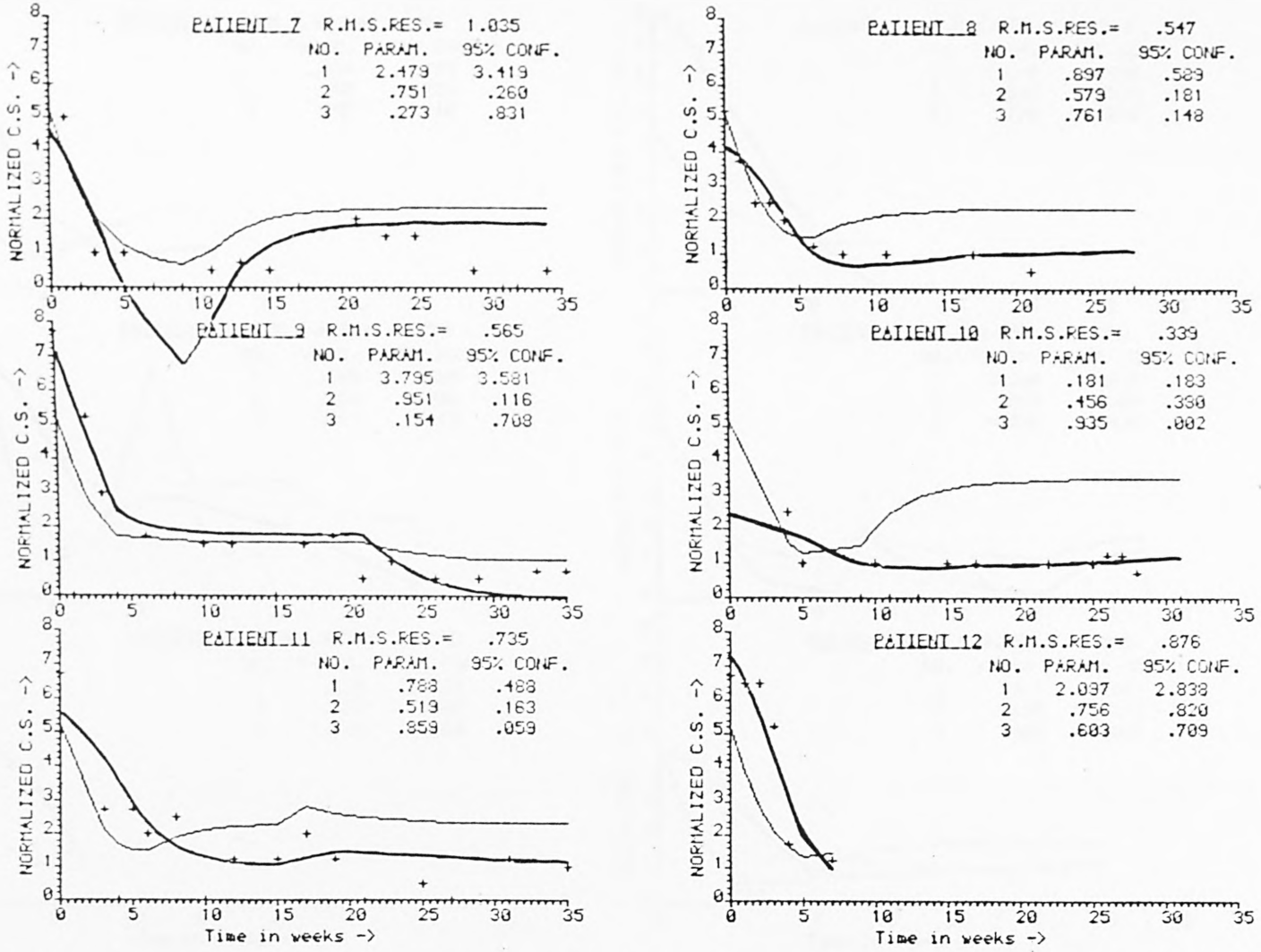
Group fit of model of clinical state including a lag term driven by individually optimised T3 responses (see figure 7.16)

Figure 7.45



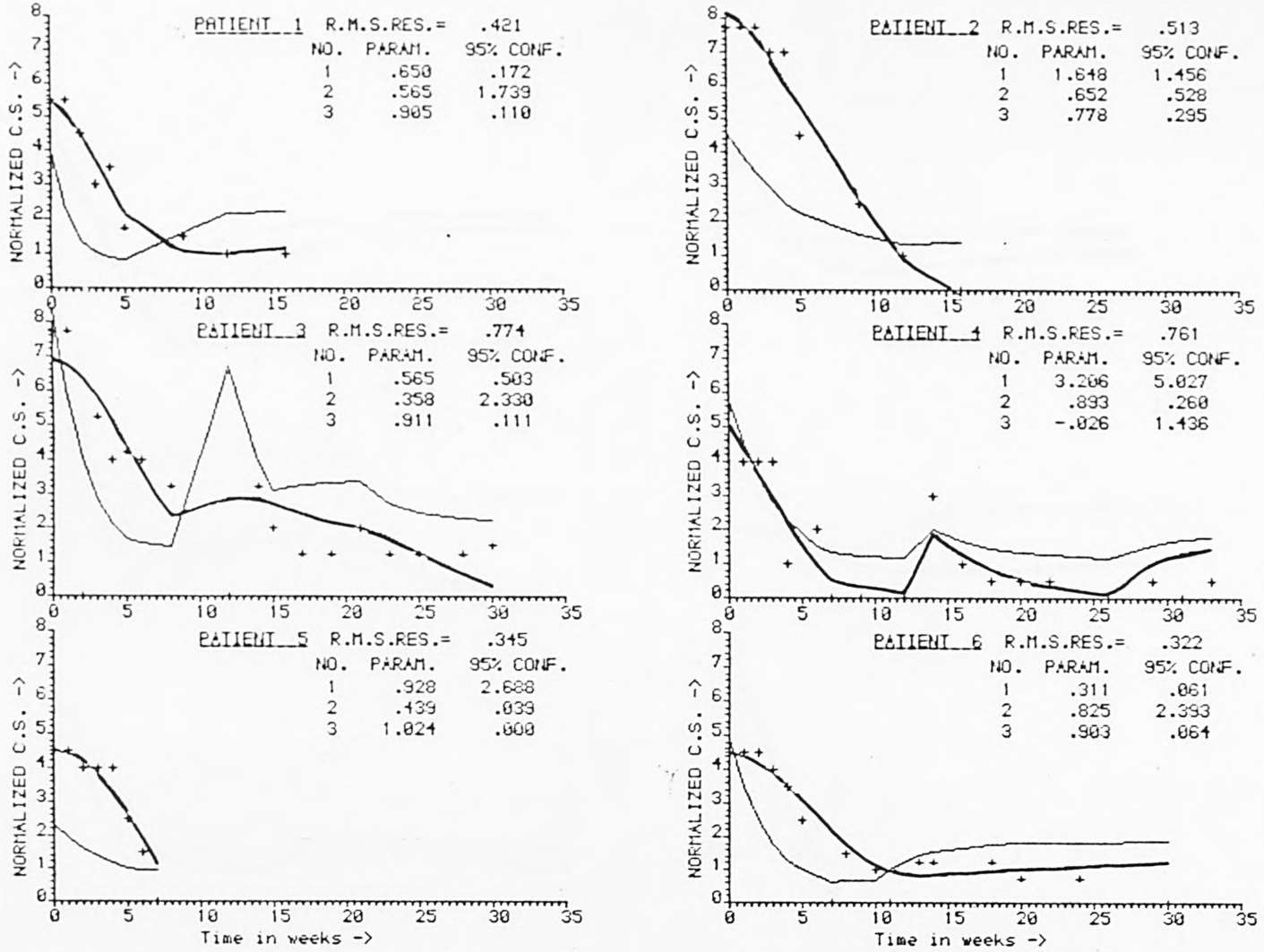
Individual fits of model of clinical state including a lag term driven by 'typical' T3 responses (see figure 7.13)

Figure 7.46



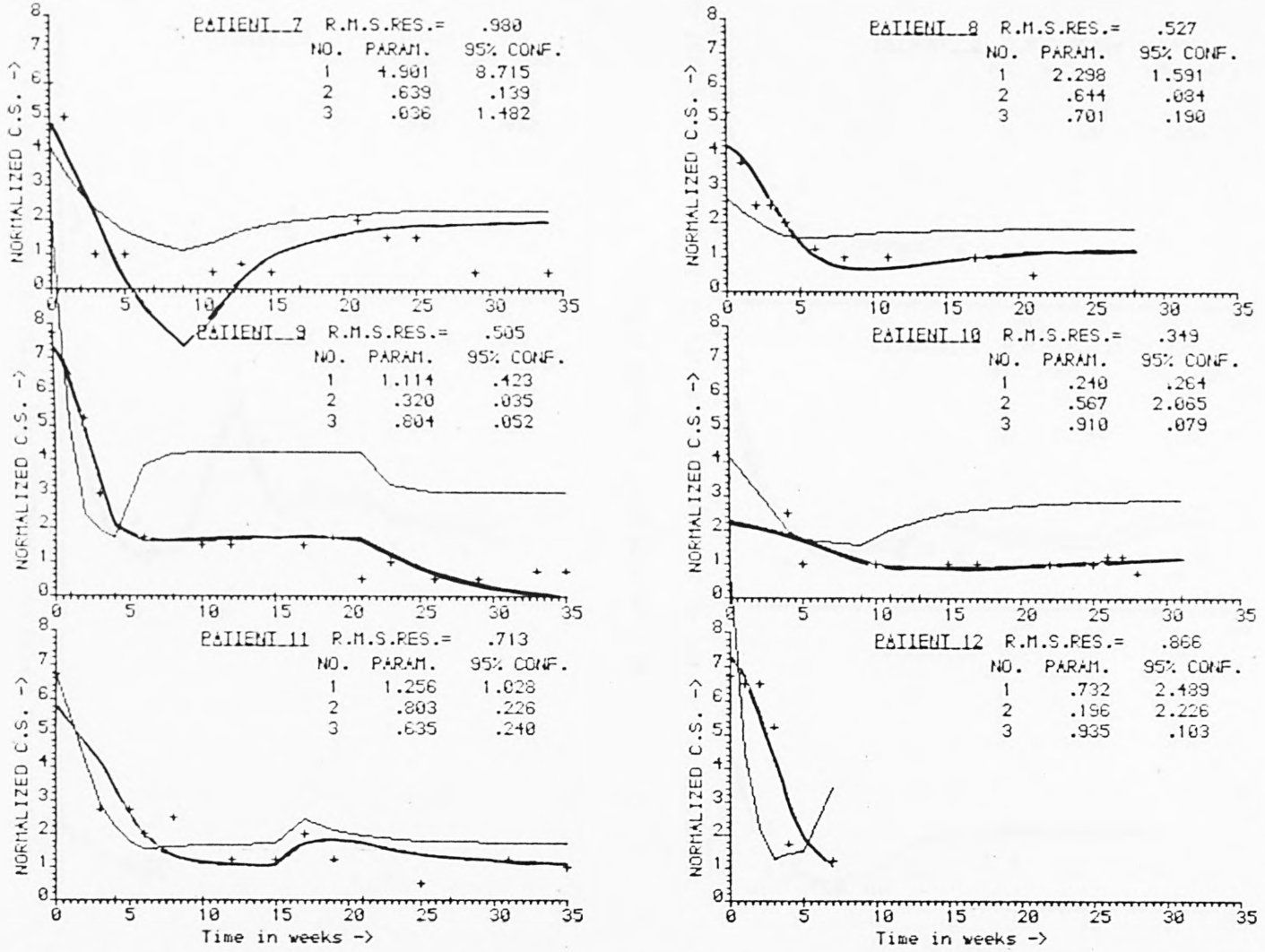
Individual fits of model of clinical state including a lag term driven by 'typical' T3 responses (see figure 7.14)

Figure 7.47



Individual fits of model of clinical state including a lag term driven by individually optimised T3 responses (see figure 7.15)

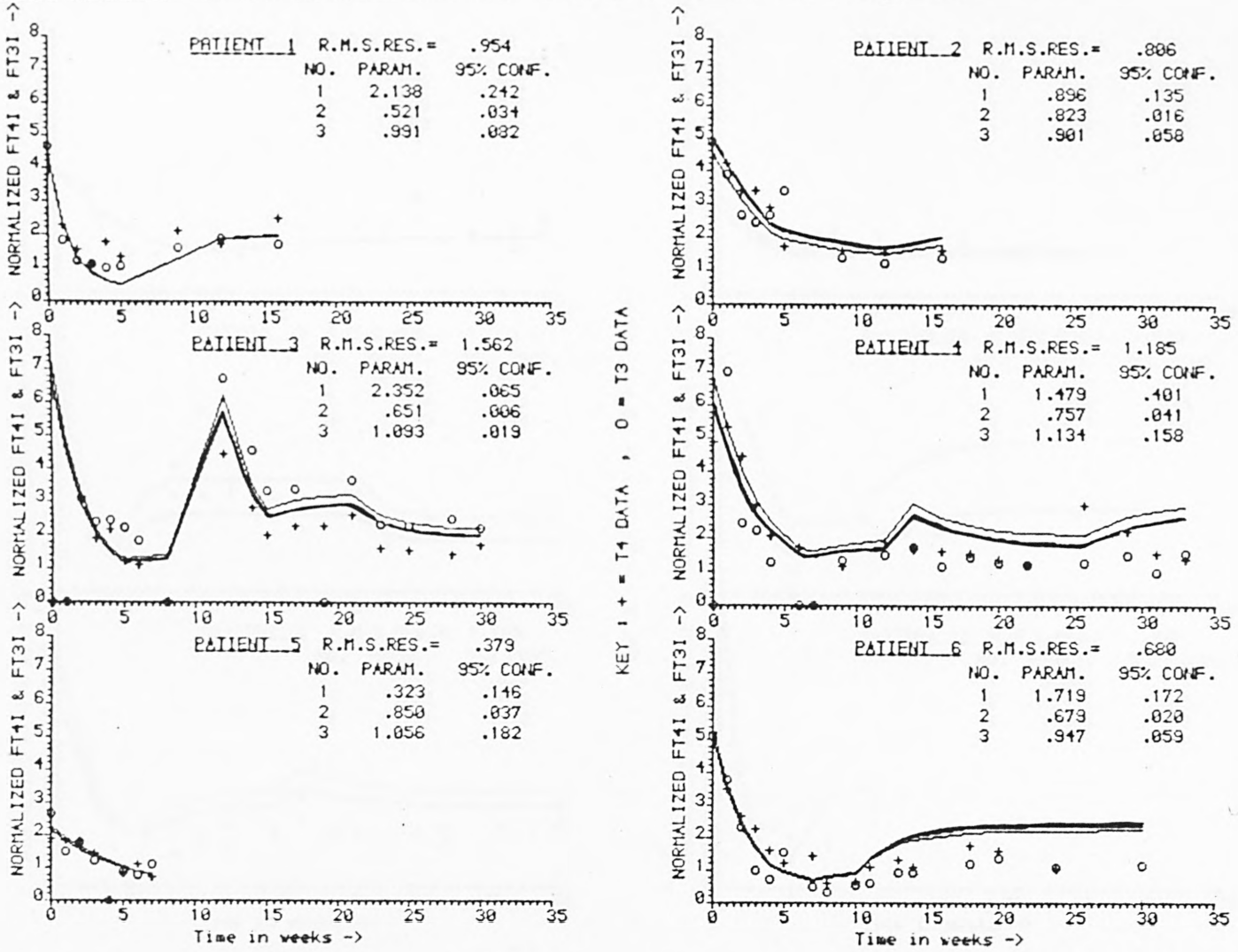
Figure 7.48



Individual fits of model of clinical state including a lag term driven by individually optimised T3 responses (see figure 7.16)

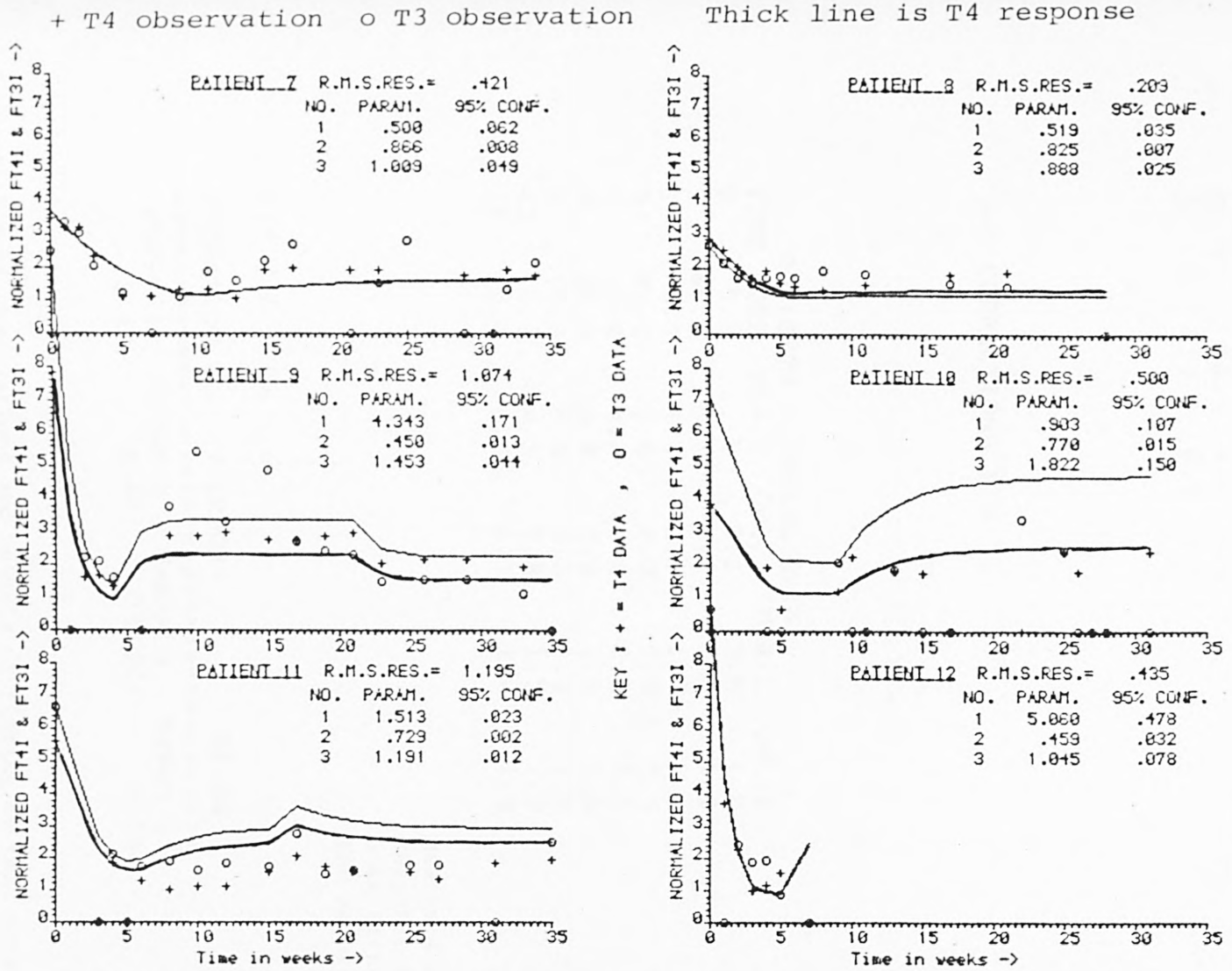
Figure 7.49

+ T4 observation o T3 observation . Thick line is T4 response



Parameter estimates and responses for thyroidal model after fitting to first five observations of T4 and T3 using 3 parameter form.

Figure 7.50



Parameter estimates and responses for thyroidal model after fitting to first five observations of T4 and T3 using 3 parameter form

Figure 7.51

PATIENTS CLINICAL DATA

PATIENT P1 DATA OVER TIME

N	TIME	DOSE	1	2
1	0	0.0	11.6	3.8
2	1	45.0	6.1	1.5
3	2	45.0	4.1	1.0
4	3	30.0	3.0	0.9
5	4	30.0	4.7	0.8
6	5	30.0	3.5	0.8
7	9	15.0	5.6	1.3
8	12	10.0	4.5	1.5
9	16	10.0	6.6	1.4

Presentation of Patient drug,T4 and T3 data from data file on text screen

ANY CORRECTIONS Y/N

PATIENTS CLINICAL DATA

TIME	DOSE	MEA.1	CAL.1	MEA.2	CAL.2
0	0.0	11.6	9.1	3.8	1.8
1	45.0	6.1	9.1	1.5	1.8
2	45.0	4.1	5.1	1.0	1.0
3	30.0	3.0	3.2	0.9	0.6
4	30.0	4.7	3.0	0.8	0.6
5	30.0	3.5	2.9	0.8	0.6
9	15.0	5.6	4.8	1.3	1.0
12	10.0	4.5	5.8	1.5	1.2
16	10.0	6.6	6.1	1.4	1.2

Measured and simulated response from model
Note screen size limits the accuracy of output

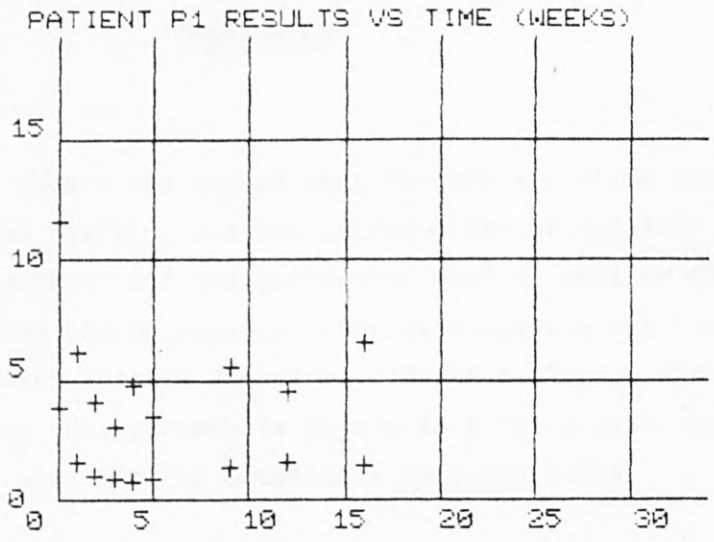
FIT O.K. Y/N

ITERATION NO. 13 ERROR= 26.88

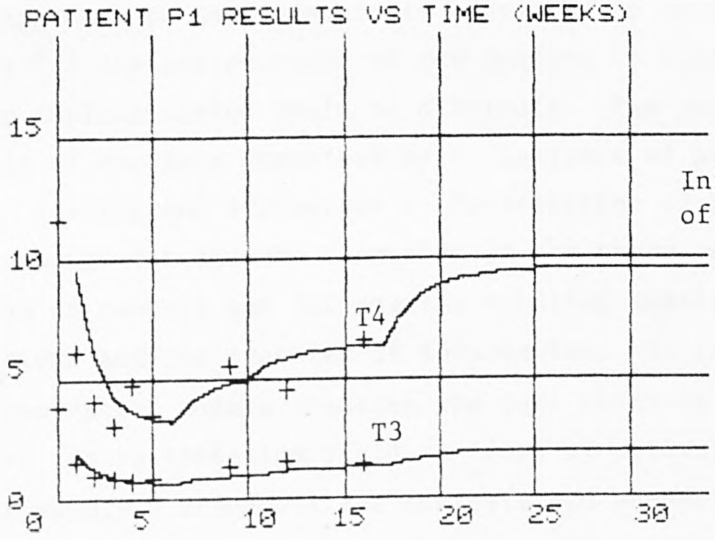
PARAM 1	PARAM 2	PARAM 3	PARAM 4
0.48	0.47	0.20	0.04

Presentation of observations and results of fitting on text screen

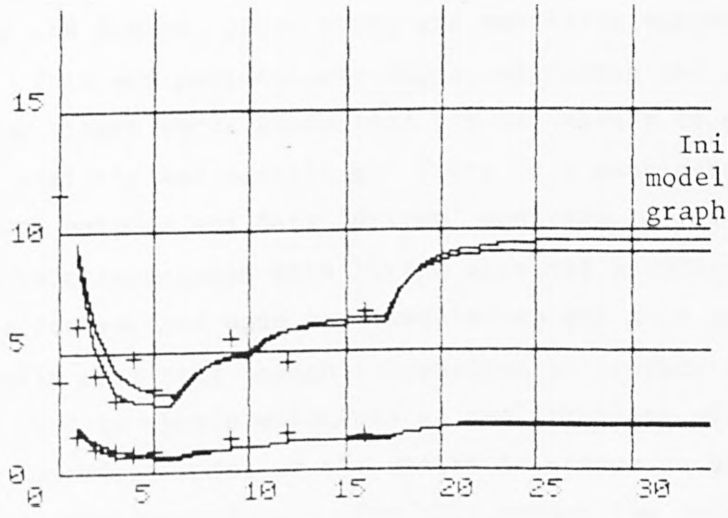
Figure 7.52



Graphics screen showing patient data and scales



Initial response of thyroidal model



Initial and fitted model responses on same graph .

Graphical presentation of patient data and model response Figure 7.5

CHAPTER 8

Conclusions

This thesis has argued that through a systems analysis of medical information handling and the introduction of suitable models to describe both the patient and the instrument used to monitor the patient state a contribution can be made to clinical chemistry and the management of patients with chronic disorders. Thyroid disease has been taken as the example but the approach is appropriate for a wide range of conditions which are monitored by occasional *in vitro* tests.

A methodology has been presented which in its emphasis upon an iterative approach to improvements in operation is particularly appropriate for the introduction of new systems to environments where a single step implementation would be difficult. The thesis shows a single cycle of the loop described by : Analysis of problem :Design of solution : Testing and Evaluation : Redefinition of Problem. Analysis of patient management and the operation of the assay service lead to the introduction of control and information handling models to describe their functions and the transfer of information. It is not suggested that such conceptual models describe the full richness of these systems or that they can in isolation yield an ideal or optimal solution. They can however supply a framework for analysis and encourage the examination of particular aspects of the system as parts of an integrated whole. This has ensured that an emphasis upon the clinical relevance of the design, pilot study and modelling subsequently undertaken. This was particularly important during the later analysis and modelling stages where guidelines are nec essary to discipline the statistical analysis and modelling. There is a considerable temptation to switch from purpose and data 'driven' analysis to the construction of elegant abstract structures with little clinical benefit. A related danger is to concentrate upon experimentation and data aquisition in the hope of finally obtaining enough information to produce a complete model. The need to obtain solutions to real problems with the available data and an imperfect model of the system is common to many problems encountered in systems science. For this reason the initial emphasis was upon evaluation of the type and quality of data that could be

provided routinely by the physician. Again an iterative approach was accepted as being necessary. and a pilot study was undertaken to establish the feasibility and usefulness of data collection. The 'data link' used in the study was subject to minor changes as a result of user experience and the conclusions of the pilot study analysis. As a consequence the 'link' has remained in use after the study was completed and has recently been applied in a study of free hormone assays - again after slight modifications to meet changed requirements . It is suggested that this iterative 'learning' approach to system implementation is more realistic than attempts to introduce an ideal final solution. A similar situation often arises in software development as the perceived needs of users change as they gain experience and recognise the potentials and problems of a new system. Indeed this thesis has seen a development in emphasis from the simplistic requirement to improve discrimination of the 'true' final diagnosis through a recognition of the inherent complexity and uncertainty of the patient state to a new aim of describing the dynamic nature of patient behaviour.

A popular method for the analysis of clinical and biochemical data has been the application of statistical models in a discriminant or pattern recognition techniques. In practice we have found that the inherent inter individual variations obscure the underlying relationships and when combined with limited amounts of data reduce the effectivness of these techniques. It is possible to include additional medical knowledge but as this usually implies historical data time series models are a more natural vehicle. Complex dynamic models while unsuitable for direct application to many clinical problems can have an important role in the resolution and selection of reduced models designed for routine clinical application. Reduced dynamic models of patient behaviour have been derived, validated and shown to have a role in the interpretation of clinical and biochemical data. A micro computer implementation of the algorithm to identify these models has been undertaken to confirm the practicality of such models The design cycle is now complete and a re-examination of the needs of the physician , the type of data available should now be undertaken in the light of these results.

The thesis has demonstrated that a contribution to the operation of

a clinical chemistry laboratory can be achieved by the collection of clinical data and the application of patient models. Chapter 4 showed that even a simple statistical analysis of clinical data can go some way to reducing assay numbers and give a substantial improvement in the screening for inconsistencies in assay results. The frequent absence of an absolute standard for a test and the lack of clinical quality control means that a patient record may serve as the only check upon the clinical value or quality of a test.

For the physician many of the benefits of clinical modelling are coincident with those of the laboratory. Probably the major single advantage is the ability of the model to integrate a large amount of uncertain data into a consistent pattern. Against this pattern anomalous results, possible failures of compliance, changes of underlying patient state , etc may readily be detected. The parameters identified may not have physical significance but they quantify the behaviour of a patient and allow automatic screening procedures to be introduced.

Considerable work remains before any model based algorithm can be expected to reliably advise upon the most suitable therapy. This thesis has attempted to show that real benefits can be obtained now by the application of models to clinical data and that an even greater potential benefits can be expected to flow from the application of these techniques.

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Appendix 1

A Program for the Identification of Clinical Models

This program is a derivative of "GIDENT" written in Fortran IV by Professor R.D. Roberts of the Department of Systems Science for the identification of non-linear dynamic models of industrial processes. It uses the N.A.G. library algorithm E04FAF for optimisation and includes a routine (PERAS) for estimation of parameter variance and the resultant uncertainty in the model output. Apart from the inclusion of the problem specific models a number of additions have been made to the original program.

(1) The graphical library GINO has been used to provide graphical presentation of model performance. Plots may be produced under user control in a number of different formats both before and after optimisation. The graphical output has been compressed by presenting six plots on the same screen, thus allowing the full set of twelve patients to appear on two screens. The figures in chapter 7 were taken directly as hard copy from the program output. As the therapy input was constant throughout the series of identifications it was decided to simplify the presentation by excluding therapy data. The full data set can be seen at the end of this Appendix. Any missing observations appear as zero values and were excluded from calculations. The predicted response was calculated at each observation point and point-to-point interpolation used to produce a continuous line. This presentation reflects the discrete nature of the difference models applied. which had a step length of a week, the minimum time between observations. It is possible to plot each variable separatly or overlay them upon the same graph. Overlaying the T3 and T4 data of chapter 7 was possible unless confidence limits were required when each was ploted separatly. The graphical presentation is controlled by three flags at the beginning of the program. 'ISEP' allows either the first set of patient data of each run, each patient's observations or each variable from each set of patient data to be plotted out separately. 'INITP' controls the plotting of the initial response before parameter optimisation. 'IVAR' selects the basic response or the 95% confidence limits.

(2) Estimation of model parameters for a group of patients can now be performed either individually for each patient in turn or simultaneously for the whole group. 'NPS' determines the number of sets of patient data that will be processed. 'NPD' determines the number of sets of patient data that will be processed simultaneously.

(3) It is possible to estimate model parameters on a reduced set of the observations made on each individual. In this work interest has centred on the identifiablity of the models used with the first few measures available. The flag 'NSIG' is used to indicate the number of measures which are to be included in the identification. The estimates of parameter variation are derived from this reduced data set by the subroutine PERAS but the resultant uncertainty in model output is calculated for the whole data set.

Apart from these additions the other major modification has been to make a range of models available at the same time and the removal of the routines used for integration of the usual differntial equation forms. This results in a considerably quicker optimisation than had been previously obtained . This method also avoids the occasional difficulties with numerical integration when, for example, step lengths approach the time constant of one equation. The cost is a loss of "physical" relevance to the parameters actually used. The time taken to identify these models is a function of model complexity, the amount of data available and the initial parameter estimates. Use of the difference equations appeared to give on order of magnitude reduction in the time taken to optimise the simple models used during initial testing.

The code for the program appears in the last pages of this appendix. The opimisation algorithm E04FAF is described in detail in the appropriate N.A.G. bullitin. The estimation of parameter variance is derived from No ton (1972) and the same method is described in the current N.A.G. reference manual.

Experience with the program suggested that while optimisation was successful estimates of the confidence limits on the model output were unrealistically optimistic. This was surprising in view of the amount of local usage the program had received. Finally a number of errors

were located in PERAS and the results quoted in the text were obtained. The confidence limits may still appear narrow but they are an estimate of the uncertainty in the fitted line and not the individual measures. This corresponds to the standard error of the mean (SEM) a statistic which indicates the uncertainty in a sample estimate of the mean. The SEM is always smaller than the standard deviation of the sample. A consequence is that the confidence limits will not necessarily lie beyond 95% of the sample points. It may be noticed that no explicit goodness of fit test was available. This would have been a greater problem when using the original non-graphical version. Even with a graphical presentation of results an overall goodness of fit test can be useful to draw attention to small systematic errors.

A fuller description of the code from which this program has been developed is available in : Roberts P.D. (1977). 'Parameter Estimation in Non-linear Dynamic Mathematical Models - User manual for subroutines IDENT and PERAS'. Departmental Research Memorandum: DSS/PDR/127 (Feb 77).

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      DIMENSION ERS(720),AJAC(720,4),X(4),
     1          A1(4,720),A2(4,4),A3(4,1),A4(4,4)
     2          ,STPR(5)
C
      COMMON /ONE/ W(5500)
      COMMON /PHIL/ PR(10),Y(4,180),MT(180),YA(4,180),WT(4,180),
     1           U(180),NXX,NYY,NPD,MTYP,NSIG,DRPR(4),PT34P(4,12),IWRT
C
      IMPLICIT DOUBLE PRECISION (A - H,O - Z)
      DATA NY/2/,NX/3/,NS/180/,NP/3/,NPD/1/,NPS/12/,IT/0/
C
C    INITIALIZE COUNTERS FLAGS AND STARTING PARAMETERS
C-------------------------------------------------------
C
C NY=NO. OF MEAS. VAR'S
C NP=NO. OF FITTED PARM'S
C NPS=NO. OF PAT'S/DATA SETS
C NPD= NO. OF CASES/PAT'S PER RUN
C MTYP=MODEL NO.
C NWPR=1 FOR NEW I.V.'S FOR P'S
C NSIGST & NSIGSP START + END NO.'S OF SIGNIF MEASURES
C NFXP=NO. OF PARAM'S IN PR( .. NP) NOT FITTED
C ISEP=0 PLOT 1'ST OF EACH RUN,=1 PLOT1 OF EACH DATA SET,=2PLOT EACH VAR
C       SEPERATLY
C IVAR =1 PLOT MODEL RESP.,=2POLOT95% CONF.LIMITS
C IWRT =0 NO INTEG MON =1 SOME =2 ALL
C
      DO 1 I=1,10
    1 PR(I)=0.1
      READ(1,5) NY,NP,NPS,NPD
    5 FORMAT(2I1,2I2)
      READ(1,5) MTYP,NWPR
      READ(1,5) NFXP,ISEP,IVAR,INITP
      READ(1,6) NSIGST,NSIGSP
      READ(1,5) IWRT
C
    6 FORMAT(2I3)
      NXX = NP  +  1
      NYY = NP  +  NFXP
      IF(MTYP.LT.5) NX = 3
      IF(MTYP.EQ.5) NX = 3
      WRITE(1,7) NFXP
    7 FORMAT(' THERE ARE ',I2,' FIXED PARAMTERS')
      IF(NFXP.GT.0) READ(1,10) (PR(I),I=NXX,NYY)
   10 FORMAT(F12.5)
C
      CALL S5600
      CALL DEVPAP(600.,300.,0)
      NXX=NX
      NYY=NY
C
C  REPEAT FOR A DECREASING NO. OF DATA POINTS (NSIG)
C-------------------------------------------------
      DO 1000 NSIGC = NSIGST,NSIGSP,-1
      NSIG =  NSIGC
      REWIND 5
      IF(MTYP.LT.5) REWIND 8
C
      DO 15 N = 1  , 12
   15 READ(8,10) (PT34P(I,N),I=1,4)
C
      WRITE(6,20) NSIG
      WRITE(7,20) NSIG
      WRITE(1,20) NSIG
   20 FORMAT(15H NO OF SIG PTS=,I3)
C
C  REPEAT FOR EACH PATIENT OR GROUP DATA
C-------------------------------------------------------
      DO 1000 IRUN=1,NPS
C
      NSIG = NSIGC
      IT=0
      TWT=0
C
      DO 17 I = 1,4
   17 DRPR(I) = PT34P(I,IRUN)
```

```
C
      DO 90 I=1,NP
      IF(NWPR.EQ.1.OR.(IRUN.EQ.1.AND.NSIG.EQ.NSIGST)) READ(1,10) STPR(I)
   90 PR(I)=STPR(I)
C
C  READ NPD SETS OF DATA EACH TERMINATED BY 999
C-------------------------------------------------
      DO 300 NPC=1,NPD
  100 IT=IT + 1
      READ(5,30)  MT(IT),(YA(N,IT),N=1,4),U(IT)
   30 FORMAT(7X,I3,4D5.0,5X,D5.0)
C
      IF (MTYP.GE.5) GOTO 150
C   NORMALIZE VARIABLES, WEIGHT MISSING OR IGNORED DATA AT 0.
C-------------------------------------------------------------
      IF(MTYP.NE.4) YA(1,IT)=YA(1,IT)/2.65
      YA(2,IT)=YA(2,IT)/81.
      YA(3,IT)=YA(3,IT)/25.
      YA(4,IT)=YA(4,IT)/4.
      IF(MTYP.EQ.2)YA(1,IT)=YA(3,IT)
      IF(MTYP.EQ.3) YA(1,IT)=YA(4,IT)
C
  150 DO 200 N=1,4
      WT(N,IT)=1.0
      IF(YA(N,IT).LT.0.0001)WT(N,IT)=0.0
      TWT=TWT+WT(N,IT)
  200 CONTINUE
C
      IF(MT(IT).NE.999) GOTO 100
  300 CONTINUE
C
C
C   DATA IN YA, WEIGHTS IN WT, NO. DATA SAMPLES=ND
C-------------------------------------------------
      IDF=TWT - NP
      ND=IT - NPD
      NS=IT
      IERS=NY*ND
      K= NP + 3 + NP/3
      IW= 2*IERS + 4*NP + IERS*NP+(NP*NP+NP)/2 + K*(2+IERS+2*NP)
      WRITE(7,40) NX,NY,ND,NS,K,IERS,IW,IDF
      WRITE(6,40) NX,NY,ND,NS,K,IERS,IW,IDF
   40 FORMAT(1X,3HNX=,I2,4H NY=,I2,4H ND=,I3,4H NS=,I3,3H K=,I3,
     1       6H IERS=,I5,4H IW=,I6,8H D OF F=,I4)
C
C
      WRITE(1,999) (PR(I),I=1,10)
  999 FORMAT(' PRS ="',10F5.2)
      CALL GIDENT(NY,NS,NX,NP,ERS,IERS,AJAC,IW,S,IFAIL,
     1            A1,A2,A3,A4,IRUN,IDF,INITP,ISEP,IVAR)
C
      IF(IFAIL.EQ.0) GOTO 500
      WRITE(1,50)
      WRITE(6,50)
      WRITE(7,50)
   50 FORMAT(23H0*** GIDENT FAILURE ***)
500   WRITE(6,60) NSIG
      WRITE(7,60) NSIG
   60 FORMAT(/,7H "NSIG=,I3,4H `` )
      IF(MTYP.EQ.1) WRITE(8,10) (PR(I),I=1,NP)
 1000 CONTINUE
      CALL DEVEND
      STOP
C
```

```
      SUBROUTINE GIDENT(NY,NS,NX,NP,ERS,IERS,AJAC,IW,S,IFAIL,
     1                  A1,A2,A3,A4,IRUN,IDF,INITP,ISEP,IVAR)
C
C         IDENTIFICATION OF NONLINEAR DYNAMIC SYSTEM WITH SEVERAL
C         OUTPUT SIGNALS
C
C         NY    = NO OF SEPARATE OUTPUT SIGNALS (INPUT)
C         NS    = NO OF SAMPLES PER OUTPUT SIGNAL (INPUT)
C         NX    = NO OF STATE VARIABLES (INPUT)
C         NP    = NO OF MODEL PARAMETERS (INPUT)
C         ERS   = IERS ARRAY OF WEIGHTED RESIDUALS (OUTPUT)
C         IERS  = DIMENSION OF ERS (INPUT) (IERS=NY*NS)
C         AJAC  = IERS,NP JACOBIAN MATRIX (OUTPUT)
C         W     = IW ARRAY OF WORKING STORE (OUTPUT)
C         IW    = DIMENSION OF W (INPUT) (IW=2*IERS+4*NP+IERS*NP+
C                 0.5*(NP*NP+NP)+K*(2+IERS+2*NP) WHERE K IS LARGEST
C                 INTEGER LESS THAN NP+3+NP/3)
C         V     = NP ARRAY OF SCALING FACTORS (INPUT)
C         S     = SUM OF SQUARE WEIGHTED RESIDUALS (OUTPUT)
C         IFAIL  = ERROR FLAG SET = 0 IF SUCCESSFULL (OUTPUT)
C         A1    = NP,IERS ARRAY OF WORKING STORE
C         A2    = NP,NP ARRAY OF WORKING STORE
C         A3    = NP,1 ARRAY OF WORKING STORE
C         A4    = NP,NP ARRAY OF WORKING STORE
C         IOPT = OPTION ON WEIGHTING SET = 1 IF SCALAR, = 0 IF TIME
C
C         USER TO SUPPLY TWO SUBROUTINES MODEL AND OUTP VIZ.
C
C         MODEL(DERX,X,T)
C         WHERE DERX = NX ARRAY OF DERIVATIVES, X = NX ARRAY OF STATES
C         AND T = CURRENT TIME. PURPOSE IS TO COMPUTE DERX GIVEN X
C
C         OUTP(T,X,Y)
C         WHERE Y = NY ARRAY OF CURRENT MODEL OUTPUTS. PURPOSE IS TO
C         COMPUTE Y GIVEN X
C
C         THE FOLLOWING NAMED COMMON BLOCK IS ALSO USED (ALSO SUPPLIED
C         BY USER
C
C         COMMON /GDNT/ PR( ),X( ),XIC( ),YA( , ),Y( , ),E( , ),C(9, ),
C                       AA(9, ),G( , ),IP( ),R( ),F( ),EBND,DT,EB( ),
C                       NXX,NIS,WT( , ),TFIN,NSS,YY( ),NYY
C
C         PR    = NP ARRAY OF MODEL PARAMETERS
C         X     = NX ARRAY OF STATE VARIABLES
C         XIC   = NX ARRAY OF INITIAL CONDITIONS ON X
C         YA    = NY,NS ARRAY OF DESIRED OUTPUTS
C         Y     = NY,NS ARRAY OF MODEL OUTPUTS
C         E     = NY,NS ARRAY OF ERRORS
C         C     = 9,NX ARRAY OF WORKING STORE
C         AA    = 9,NX ARRAY OF WORKING STORE
C         G     = NX,NX ARRAY OF WORKING STORE
C         IP    = NX INTEGER ARRAY OF WORKING STORE
C         R     = NX ARRAY OF WORKING STORE
C         F     = NX ARRAY OF WORKING STORE
C         EBND  = INTEGRATION ERROR BOUND
C         DT    = SAMPLING INTERVAL
C         EB    = NX ARRAY OF ERROR BOUNDS
C         NXX   = NUMBER OF STATE VARIABLES (NXX=NX)
C         NIS   = NUMBER OF INTEGRATIONS PER SAMPLE
C         WT    = NY,NS ARRAY OF WEIGHTING COEFFICIINTS
C         TFIN  = FINAL CPU TIME
C         NSS   = NUMBER OF SAMPLES (NSS=NS)
C         YY    = NY ARRAY OF CURRENT MODEL OUTPUTS
C         NYY   = NUMBER OF OUTPUTS (NYY=NY)
C-----------------------------------------------------------------------
      DIMENSION ERS(IERS),AJAC(IERS,NP),V(10),A1(NP,IERS),
     1      A2(NP,NP),A3(NP,1),A4(NP,NP),ERR(20,4),ERRSQ(20,4),
     2          SERR(20,4),SSERR(20,4),NC(20,4),YAMN(20,4)
C
C         USER TO INSERT COMMON /GDNT/ HERE
C
      COMMON /ONE/ W(5500)
      COMMON /PHIL/ PR(10),Y(4,180),MT(180),YA(4,180),WT(4,180),
     1              U(180),NXX,NYY,NPD,MTYP,NSIG,DRPR(4),PT34P(4,12),IWR
C
```

```
      EXTERNAL FUNCT,MONIT
      IMPLICIT DOUBLE PRECISION (A-H,O-Z)
      DATA DSTEP/0.01/,MAXIT/150/,IPRNT/1/
      WRITE(1,1)
    1 FORMAT(10HIN GIDENT )
      EPS=0.001
      ALF=0.001
      DO 5 I=1,NP
    5 V(I)  =  0.1
C
C     INITIAL RESPONSE AND DATA CHECK
C-------------------------------------------------------
      WRITE(6,200) NY,NS
  200 FORMAT(28HONUMBER OF OUTPUT SIGNALS = ,I2/20HO NUMBER OF SAMPLES
     1       2H= ,I2)
C
      WRITE(6,210) MAXIT,IPRNT,EPS,ALF,DSTEP,(PR(II),II=1,NP)
  210 FORMAT(17HOINITIAL RESPONSE,2I4,7F10.3)
      CALL FUNCT(IERS,NP,PR,ERS)
      S=0.0
      DO 7 I=1,IERS
    7 S = S  +  ERS(I)**2
      IF(IRUN.NE.1) GOTO 240
      DO 8 J=1,NY
    8 WRITE(6,211) J,(Y(J,I),I=1,NS)
  211 FORMAT(17HOMODEL OUTPUT NO.,I2/(1H ,8E15.6))
  240 WRITE(6,212) S
      WRITE(7,212) S
  212 FORMAT(44HOINITIAL SUM OF WEIGHTED SQUARE RESIDUALS = ,E15.6)
C
      IF(INITP.EQ.1) CALL PLOTER(ERS,A3,IERS,S,NP,IRUN,ISEP,0)
C
C        OPTIMISATION
C-------------------------------------------------------
      IFAIL=1
      IF(IPRNT.NE.0) WRITE(6,213)
  213 FORMAT(21HOOPTIMISATION MONITOR)
      JERS  =  IERS
      IF(NSIG.LT.NS) JERS  =  NYY*NSIG
      CALL E04FAF(JERS,NP,PR,ERS,S,EPS,ALF,V,W,IW,FUNCT,MONIT,IPRNT,
     1            MAXIT,IFAIL)
C        ERROR MESSAGE
      IF(IFAIL.LT.1) GOTO 10
      WRITE(1,214) MAXIT
      WRITE(6,214) MAXIT
      WRITE(7,214) MAXIT
  214 FORMAT(15HO*** MORE THAN ,I5,15H ITERATIONS ***)
C
C        FINAL  RESPONSE
C-------------------------------------------------------
   10 CONTINUE
      I     =  NSIG
      NSIG  =  999
C
      CALL FUNCT(IERS,NP,PR,ERS)
C
      NSIG  =  I
C
      WRITE(7,215)
      WRITE(6,215)
  215 FORMAT('  FINAL RESPONSE AND PARAMETERS')
C
C
      DO 70 K=1,NY
       NC(IRUN,K)    = 0
       YAMN(IRUN,K)  = 0
       SERR(IRUN,K)  = 0
   70  SSERR(IRUN,K) = 0
      DO 11 J=1,NS
      DO 60 K=1,NY
       ERR(IRUN,K) = 0
       ERRSQ(IRUN,K)= 0
       IF(YA(K,J).LT.0.01) GOTO 60
       NC(IRUN,K)    =  NC(IRUN,K)    +  1
       YAMN(IRUN,K) =  YA(K,J)  +  YAMN(IRUN,K)
       ERR(IRUN,K)  =  YA(K,J)  -  Y(K,J)
```

```
      ERRSQ(IRUN,K) =  ERR(IRUN,K)*ERR(IRUN,K)
      SERR(IRUN,K)  =  SERR(IRUN,K)    + ERR(IRUN,K)
      SSERR(IRUN,K) =  SSERR(IRUN,K)   + ERRSQ(IRUN,K)
   60 CONTINUE
      WRITE(7,220) IRUN,J,MT(J),(YA(K,J),Y(K,J),ERR(IRUN,K),
     +             ERRSQ(IRUN,K),K=1,NY),U(J)
   11 WRITE(6,220) IRUN,J,MT(J),(YA(K,J),Y(K,J),ERR(IRUN,K),
     +             ERRSQ(IRUN,K),K=1,NY),U(J)
  220 FORMAT(3I4,2(4(F8.2,1X),4X),F6.1)
C
      IDF    =  0
      TSSER  =  0.
      DO 80 K=1,NY
       N       =  NC(IRUN,K)
       IDF     =  IDF  +  N
       IF(N.LT.1) GOTO 301
       YAMN(IRUN,K) =  YAMN(IRUN,K)/N
       ERRM    =  SERR(IRUN,K)/N
       IF(N.LT.2) GOTO 301
       SDERR   =  DSQRT(SSERR(IRUN,K)/(N-1))
       CVERR   =  100*SDERR/YAMN(IRUN,K)
       TSSER   =  TSSER  +  SSERR(IRUN,K)
  301  IF(N.LT.2) WRITE(6,302)
       IF(N.LT.2) WRITE(7,302)
  302  FORMAT(' **** INSUFFICIEENT DATA IGNORE RESULTS ``**')
       WRITE(1,300) K,N,YAMN(IRUN,K),SERR(IRUN,K),ERRM,
     +              SSERR(IRUN,K),SDERR,CVERR
       WRITE(6,300) K,N,YAMN(IRUN,K),SERR(IRUN,K),ERRM,
     +              SSERR(IRUN,K),SDERR,CVERR
       WRITE(7,300) K,N,YAMN(IRUN,K),SERR(IRUN,K),ERRM,
     +              SSERR(IRUN,K),SDERR,CVERR
  300 FORMAT(' VAR ',I1,' NO. MEAS.=',I2,' MEAN=',F8.3,' ERR SUM=',
     +       F8.3,' MEAN ERR=',F8.3,' SUM SQ. ERR.=',F8.3,
     +       ' S.D. ERR.=',F8.3,' C.V. ERR.=',F8.3)
   80 CONTINUE
C
      IDF    =  IDF  -  1
      IF(IDF.GT.0) TSDER  =  DSQRT(TSSER/IDF)
      WRITE(1,216) NSIG,S,TSSER,TSDER,IDF
      WRITE(6,216) NSIG,S,TSSER,TSDER,IDF
      WRITE(7,216) NSIG,S,TSSER,TSDER,IDF
  216 FORMAT(' OBSERATIONS =` ',I3,' FITTED TO GIVE S.SQ. WT. ERR=',
     +       F9.3,' OVERALL S.SQ. ERR.=',F9.3,' OVERALL S.D. =',
     +        F9.3,' DEG OF F.=',I3)
C
      IF(IRUN.NE.12) GOTO 85
C
      I  =  IRUN  +  1
      DO 83 K=1,NY
        DO 82 J=1,IRUN
           NC(I,K)  =     NC(I,K)  +  NC(J,K)
         YAMN(I,K)  =   YAMN(I,K)  +  YAMN(J,K)*NC(J,K)
        SSERR(I,K)  =  SSERR(I,K)  +  SSERR(J,K)
   82   CONTINUE
        ERRM  =  YAMN(I,K)/NC(I,K)
        SDERR =  DSQRT( SSERR(I,K)/(NC(I,K) - 1) )
        CVERR =  100*SDERR/ERRM
        WRITE(6,221) NC(I,K),YAMN(I,K),SSERR(I,K),
     +               ERRM,SDERR,CVERR
        WRITE(7,221) NC(I,K),YAMN(I,K),SSERR(I,K),
     +               ERRM,SDERR,CVERR
  221 FORMAT(' TOT.NO.SAMPLES=',I3,' TOTAL=',F10.2,
     + ' TOTAL S.S.ERR=',F10.2,' MEAS.MEAN=',F10.3,
     + ' OVERALL S.D.=',F10.3,' OVERALL C.V.=',F5.1)
C
   83 CONTINUE
C
   85 ND  =  NS  -  1
C
C        SENSITIVITY ANALYSIS
C-------------------------------------------------------------
      WRITE(6,217)
  217 FORMAT(22HOACCURACY OF ESTIMATES)
      DO 12 I=1,NP
   12 V(I)=DSTEP*PR(I)
C
```

```
      IF(NP.GE.5) GOTO 255
      IF(IDF.GT.2)
     + CALL PERAS(JERS,NP,PR,ERS,S,V,FUNCT,AJAC,A1,A2,A3,A4,IDF)
C
      WRITE(1,218) NSIG,IRUN
      WRITE(6,218) NSIG,IRUN
      WRITE(7,218) NSIG,IRUN
      DO 90 I=1,NP
       CVP    =   100*A3(I,1)/PR(I)
      WRITE(1,219) I,PR(I),A3(I,1),CVP,(A4(I,J),J=1,NP)
      WRITE(6,219) I,PR(I),A3(I,1),CVP,(A4(I,J),J=1,NP)
      WRITE(7,219) I,PR(I),A3(I,1),CVP,(A4(I,J),J=1,NP)
   90 CONTINUE
  218 FORMAT(' NO. OF DATA POINTS INCLUDED=',I3,' PATIENT NO.=',I3,
     + //,' PARAM.NO.   PARAM.VAL.  95% CONFL.   CONFL. AS %',
     + '       COVARIANCE MATRIX')
  219 FORMAT(4X,I7,3F12.3,6F10.2)
C
       IF(IDF.LT.1) GOTO 305
C
C    CALCULATE RESIDUAL VARIANCES & 95% CONF. LIMITS
C    -----------------------------------------------
C
      B  =  2*S/IDF
      CONFL = 0.95
      A  =  G01CAF(CONFL,IDF,IFAIL)
C
      NSIG = 999
      CALL JACOB(NP,PR,IERS,AJAC)
C
C  RESTORE OUTPUT (Y) TO BEST FIT (DISTUR. BY JAC.) BEFORE ERS RESET
C
      CALL FUNCT(IERS,NP,PR,ERS)
C
C
      DO 99 K=1,NP
      WRITE(6,243) K,(AJAC(I,K),I=1,IERS)
  243 FORMAT(10(10H AJAC I BY,I1,12F10.4))
   99 CONTINUE
C
      DO 40 K = 1,IERS
        W(K)  = 0.
        DO 30 I = 1,NP
          D   = 0.
          DO 20 J = 1,NP
   20         D = D  +  AJAC(K,J) * A4(I,J)
C
   30     W(K)  =  W(K)  +  D*AJAC(K,I)*B
C
   40   ERS(K)  =  A*DSQRT(W(K))

  255  CONTINUE
C
      WRITE(1,244) (ERS(K),K=1,IERS)
      WRITE(6,245) (ERS(K),K=1,IERS)
  244 FORMAT(10(6F10.5,/))
245   FORMAT(10H 95% CONF ,10F10.5)
C
C
  305 CALL PLOTER(ERS,A3,IERS,TSDER,NP,IRUN,ISEP,IVAR)
C
      RETURN
      END
C
C
C=============================================================
C
      SUBROUTINE PLOTER(E,A3,IERS,S,NPAR,IRUN,ISEP,IVAR)
      DIMENSION X(180),Z1(180),Z2(180),NC(4),A3(NPAR,1),E(IERS),ZO(180
      COMMON /PHIL/ PR(10),Y(4,180),MT(180),YA(4,180),WT(4,180),
     1       U(180),NXX,NYY,NPD,MTYP,NSIG,DRPR(4),PT34P(4,12),IWRT
      DOUBLE PRECISION A3,PR,Y,YA,S,WT,U,E
      WRITE(1,2001)
 2001  FORMAT(10H IN PLOT  )
      IPLOT=IPLOT+1
C PLOTTING OF DATA POINTS (YA) BY GRASYM & MODEL POINTS Y BY GRAPOL
```

```
C-----------------------------------------------------------------
      NY = NYY
      NN = 2
      M  = MTYP
      IPT= IRUN
C
      IF(ISEP.EQ.0) CALL SCLAB(A3,S,NPAR,IPT,M,IX,IY)
      YER = 0.
C
      DO 50 I1=1,NN
   50 NC(I1) = 1
C
      DO 500 IP = 1,NPD
      IPT = IP + IRUN - 1
      IF(ISEP.EQ.1) CALL SCLAB(A3,S,NPAR,IPT,M,IX,IY)
C
      DO 400 J = 1,NN
      IF(ISEP.EQ.2) CALL SCLAB(A3,S,NPAR,IPT,M,IX,IY)
      IF(J.EQ.1) NSYM = 3
      IF(J.EQ.2) NSYM = 7
      CALL PENSEL(J,0,0.)
       NPT = 0
  100    NPT = NPT + 1
         X(NPT)=FLOAT(MT(NC(J)))
          YT       = Y(J,NC(J))
          Z1(NPT) = YT
          IF(IVAR.NE.2) GOTO 200
          K    = (NC(J) - IP)*NYY + J
          Z0(NPT) = YT - E(K)
          Z1(NPT) = YT + E(K)
  200    Z2(NPT)=YA(J,NC(J))
         NC(J) = NC(J)  +  1
         IF(MT(NC(J)).NE.999) GOTO 100
C
       IF(NPT.LT.1) GOTO 300
C
       IF(MTYP.EQ.1.OR.J.EQ.1) CALL GRASYM(X,Z2,NPT,NSYM,0)
       CALL GRAPOL(X,Z1,NPT)
       IF(IVAR.EQ.2) CALL GRAPOL(X,Z0,NPT)
  300  NC(J) = NC(J) + 1
      CALL CHAMOD
      IF(IX.EQ.2.AND.IY.EQ.3.AND.IVAR.EQ.2) CALL PHALT
  400 CONTINUE
      IF(IX.EQ.2.AND.IY.EQ.3.AND.IVAR.EQ.1) CALL PHALT
  500 CONTINUE
      RETURN
      END
C-----------------------------------------
C
      SUBROUTINE SCLAB(A3,S,NPAR,IP,MTYP,IX,IY)
C
      DIMENSION A3(NPAR,1)
      COMMON /PHIL/ PR(10)
      DOUBLE PRECISION PR,S,A3
C
      SS = S
      IX = IX + 1
      IF(IX.EQ.3) IX = 1
      IF(IX.EQ.1) IY = IY + 1
      IF(IY.EQ.4) IY = 1
C
      IF(IX.EQ.1) XPOS = 15.
      IF(IX.EQ.2) XPOS = 200.
C
      YPOS = 13.  +  81.*(3 - IY)
C
      WRITE(1,1000) IX,IY,XPOS,YPOS
1000  FORMAT(8H IN SCLA,2I4,2F10.0)
C
C
      XHEAD  =  7.0
      IF(MTYP.EQ.4) XHEAD  = 90.
      CALL PENSEL(0,0,0.)
      WRITE(1,2000)XPOS,MTYP
 2000  FORMAT(5H XPOS,F10.1,I4)
      CALL AXIPOS(0,XPOS,YPOS,140.,1)
```

```
      CALL AXIPOS(0,XPOS,YPOS,72.,2)
      IF(MTYP.NE.4)CALL AXISCA(3,7,0.,35.,1)
      IF(MTYP.EQ.4)CALL AXISCA(3,9,0.,180.,1)
      IF(MTYP.NE.4)CALL AXISCA(3,8,0.,8.,2)
      IF(MTYP.EQ.4)CALL AXISCA(3,8,0.,16.,2)
      CALL AXIDRA(2,1,1)
      CALL AXIDRA(-2,-1,2)
      CALL GRAMOV(10.,7.6)
      CALL CHAHOL(10HPATIENT *.)
      CALL CHAINT(IP,2)
      CALL CHAHOL(15H  R.M.S.RES.=*.)
      CALL CHAFIX(SS,7,3)
      CALL GRAMOV(10.,7.6)
      CALL CHAHOL(12H          *.)
      IF(IY.NE.3) GOTO 50
      CALL GRAMOV(10.,-1.3)
      IF(MTYP.NE.4)CALL CHAHOL(20HT*LIME IN WEEKS -¨*.)
      IF(MTYP.EQ.4)CALL CHAHOL(20HT*LIME IN MINS. -¨*.)
      IF(IX.NE.2) GOTO50
      CALL GRAMOV(-6.,7.)
      CALL CHAANG(90.)
      IF(MTYP.LT.1.1)
     + CALL CHAHOL(35HKEY : + = T4 DATA  ,  0 = T3 DATA*.)
      CALL CHAANG(0.)
   50 CALL GRAMOV(-2.,0.8)
      CALL CHAANG(90.)
      IF(MTYP.LT.1.9) CALL CHAHOL(28HNORMALIZED FT4I & FT3I -¨ *.)
      IF(MTYP.EQ.2) CALL CHAHOL(19HNORMALIZED TSH -¨*.)
      IF(MTYP.EQ.3) CALL CHAHOL(20HNORMALIZED C.S. -¨*.)
      CALL CHAANG(0.)
C
C-----------------------------------------
C
C
      IF(MTYP.LT.4)CALL GRAMOV(17.3,6.9)
      IF(MTYP.EQ.4)CALL GRAMOV(20.,15.)
      CALL CHAHOL(26H NO.  PARAM.   95% CONF.*.)
      DO 100 I=1,NPAR
      P=PR(I)
      SD=A3(I,1)
      YPOS=6.8-I*0.6
      XXPOS = 18.
      IF(MTYP.EQ.4) XXPOS = 22.
      YYPOS = YPOS
      IF(MTYP.EQ.4) YYPOS = YPOS + 10.
      CALL GRAMOV(XXPOS,YYPOS)
      CALL CHAINT(I,2)
      CALL CHAFIX(P,9,3)
      CALL CHAFIX(SD,9,3)
  100 CONTINUE
      CALL GRAMOV(0.,0.)
      CALL CHAMOD
      RETURN
      END
C=============================================================
      SUBROUTINE PHALT
C
C A ROUTINE TO HALT PROCESSING AT SCREEN-FULL
C THEN CLEAR-SCREEN AND CONTINUE AFTER "START"
C
      PAUSE
      CALL PICCLE
      RETURN
      END
C
C=============================================================
C
C
      SUBROUTINE MONIT(IERS,NP,P,S,ITERC,SING,LIM)
      LOGICAL SING,LIM
      DIMENSION P(10)
      IMPLICIT DOUBLE PRECISION (A-H,O-Z)
      WRITE(6,200) ITERC,S,(P(I),I=1,NP)
  200 FORMAT(7H ITER =,I5,7H SES = ,E15.6,14H PARAMETERS = ,4E15.6/
     1      (1H ,47X,4E15.6))
      IF(SING) WRITE(6,201)
```

```
  201 FORMAT(26H *** LINEAR DEPENDENCE ***)
      IF(LIM) WRITE(6,202)
  202 FORMAT(33H *** PARAMETER CHANGE LIMITED ***)
      RETURN
      END
C
C
C=================================================================
C
C  MODEL SUBROUTINES CALLED FROM FUNCT
C
C*****************************************************************
C
      SUBROUTINE FUNCT(IERS,NP,P,ERS)
C
C        OPTIMISATION SUBROUTINE WHICH CALCULATES WEIGHTED RESIDUALS
C        E(I) AS FUNCTIONS OF MODEL PARAMETERS
C
      DIMENSION P(10),ERS(IERS),X(5)
      INTEGER T
      COMMON /ONE/ W(5500)
      COMMON /PHIL/ PR(10),Y(4,180),MT(180),YA(4,180),WT(4,180),
     1          U(180),NXX,NYY,NPD,MTYP,NSIG,DRPR(4),PT34P(4,12),IWRT
      IMPLICIT DOUBLE PRECISION (A-H,O-Z)
      IT= NP + 1
      DO 40 I=IT,10
   40 P(I) = PR(I)
      IT = 1
      IF(MTYP.EQ.1.AND.NP.EQ.3) P(4)=0.081
      DO 100 NPS=1,NPD
      IF(MT(IT).EQ.999)GOTO 90
C
      DO 50 I = 1,4
   50 IF(NPD.GT.1) DRPR(I)  =  PT34P(I,NPS)
C
      IF(MTYP.EQ.1) CALL T34MOD(IT,NPS,IERS,NP,P,ERS)
      IF(MTYP.EQ.2) CALL TSHMOD(IT,NPS,IERS,NP,P,ERS)
      IF(MTYP.EQ.3) CALL CSTMOD(IT,NPS,IERS,NP,P,ERS)
      IF(MTYP.EQ.4) CALL PITMOD(IT,NPS,IERS,NP,P,ERS)
      IF(MTYP.EQ.5) CALL DIFMOD(IT,NPS,IERS,NP,P,ERS)
C
C
   90 IT=IT + 1
  100 CONTINUE
      RETURN
      END


C=================================================================
C   END OF FUNCT WHICH CALLS MODELS - START OF INDIVIDUAL MODELS
C-----------------------------------------------------------------
C
C
      SUBROUTINE T34MOD(IT,NPS,IERS,NP,P,ERS)
C   ======================================
C
      DIMENSION P(10),ERS(IERS),X(5)
      INTEGER T
      COMMON /PHIL/ PR(10),Y(4,180),MT(180),YA(4,180),WT(4,180),
     1          U(180),NXX,NYY,NPD,MTYP,NSIG,DRPR(4),PT34P(4,12),IWRT
      IMPLICIT DOUBLE PRECISION(A-H,O-Z)
C
C
      X(1) = YA(1,IT)
      X(2) = YA(1,IT)
      T    = MT(IT)  -  40
      NC   =  1
C
C     REPEAT UNTIL T = 999 OR NC ¨ NSIG
C     ---------------------------------
  100 CONTINUE
C
      GT4 = P(1)*EXP( -P(4)*U(IT) )  +  P(2)*X(1)
      PT4 = GT4
      PT3 = P(3)*PT4
C
```

```
C
      X(1) = GT4
      X(2) = PT4
      X(3) = PT3
      T    =  T    +   1
C
      IF(T.NE.MT(IT)) GOTO 100
C
      Y(1,IT) = PT4
      Y(2,IT) = PT3
      DO 200 I=1,NYY
      K = (IT - NPS)*NYY  +  I
200   ERS(K) = (Y(I,IT)  -  YA(I,IT))*WT(I,IT)
C
      NC  =  NC  +  1
  300 IT  =  IT  +  1
      IF(MT(IT).NE.999.AND.NC.LT.NSIG) GOTO 100
      IF( MT(IT).NE.999) GOTO 300
C
      RETURN
      END


C=============================================================
C
      SUBROUTINE TSHMOD(IT,NPS,IERS,NP,P,ERS)
C     ======================================
C
      DIMENSION P(10),ERS(IERS),X(5)
      INTEGER T
      COMMON /PHIL/ PR(10),Y(4,180),MT(180),YA(4,180),WT(4,180),
     1           U(180),NXX,NYY,NPD,MTYP,NSIG,DRPR(4),PT34P(4,12),IWRT
      IMPLICIT DOUBLE PRECISION (A-H,O-Z)
C
      X(1) = YA(3,IT)
      X(4) = DRPR(1)/(1. -  DRPR(2))
      X(3) = DRPR(3)*X(4)
      T    = MT(IT)  -  40
      NC   =  1
C
C   REPEAT UNTIL T = 999 OR NC ¨ NSIG
C-------------------------
  100 CONTINUE
C
      T4  =  DRPR(1)*EXP( -DRPR(4)*U(IT) )  +  DRPR(2)*X(4)
      T3  =  DRPR(3)*T4
C
      TSH  =  P(1) /(  (T3 - P(4))**P(2) )  +    P(3)*X(1)
C
      X(1)  =  TSH
      X(3) =  T3
      X(4) =  T4
       T   =  T  +  1
      IF(T.NE.MT(IT)) GOTO 100
C
      Y(1,IT) = TSH
      Y(2,IT) = T3
C
      K =  IT - NPS + 1
      ERS(K) = (Y(1,IT) - YA(3,IT))*WT(3,IT)
C
      IT  =  IT  +  1
      NC  =  NC  +  1
      IF(MT(IT).NE.999.AND.NC.LT.NSIG) GOTO 100
C
      RETURN
      END
C


C=============================================================
C
      SUBROUTINE CSTMOD(IT,NPS,IERS,NP,P,ERS)
C     ======================================
C
      DIMENSION P(10),ERS(IERS),X(5)
```

```
      INTEGER T
      COMMON /PHIL/ PR(10),Y(4,180),MT(180),YA(4,180),WT(4,180),
     1          U(180),NXX,NYY,NPD,MTYP,NSIG,DRPR(4),PT34P(4,12),IWRT
      IMPLICIT DOUBLE PRECISION (A-H,O-Z)
C
      X(1) = Y(4,IT)
      X(4) = DRPR(1)/(1. - DRPR(2))
      X(3) = DRPR(3)*X(4)
C
      T    =  MT(IT)  -  90
      NC   =  1
C
  100 CONTINUE
C
      T4   =  DRPR(1)*EXP(-DRPR(4)*U(IT))  +  DRPR(2)*X(4)
      T3   =  DRPR(3)*T4
C
       CS  =  P(1)*ALOG(P(2)*T3)  +  P(3)*X(1)
C
      X(1) = CS
      X(3) = T3
      X(4) = T4
      T    = T  +  1
      IF(T.NE.MT(IT)) GOTO 100
C
      Y(1,IT) = CS
      Y(2,IT) = T3
      K = 1 - NPS + IT
      ERS(K) = (Y(1,IT) - YA(4,IT))*WT(4,IT)
C
      IT   =  IT  +  1
      NC   =  NC  +  1
      IF (MT(IT).NE.999.AND.NC.LT.NSIG) GOTO 100
C
      RETURN
      END


C=======================================================
C
C
C
      SUBROUTINE PITMOD(IT,NPS,IERS,NP,P,ERS)
C     ======================================
C
      DIMENSION P(10),ERS(IERS),X(5)
      INTEGER T
      COMMON /PHIL/ PR(10),Y(4,180),MT(180),YA(4,180),WT(4,180),
     1          U(180),NXX,NYY,NPD,MTYP,NSIG,DRPR(4),PT34P(4,12),IWRT
      IMPLICIT DOUBLE PRECISION (A-H,O-Z)
C
C    INITIALIZATION
C    --------------
C
        P1   =  P(1)
        P2   =  P(2)
        P3   =  P(3)
C
      PTSHS  =  1.
        P8   =  0.988
        P7   =  4400
      GTSHS  =  130000
C
      PTRHS  =  P1 / ( 1. - P3 )
        P5   =  PTSHS * P7 * (1. - P8)
        P6   =  P5 / ( PTRHS * GTSHS )
         X(1)   =   PTRHS
         X(2)   =   GTSHS
         X(3)   =   PTSHS
C
C---------------------------------------
C
C
C
      T    =  MT(IT)  -  50
      NC   =  1
```

```
C
C    REPEAT UNTIL T = 999 OR NC ¨ NSIG
C    ---------------------------------
  100 CONTINUE
C
       UIN  =  U(IT)
       IF(T.GT.1) UIN  =  0.
C
       PTRH  =  P1   +   P2 * UIN    +   P3 * X(1)
       IF(PTRH.LT.1.) PTRH  =  1.
C
       GTSH  =  P5   +   (1.  -  P6 * X(1) ) * X(2)
       IF(GTSH.LT.0.) GTSH  =  0.
C
       PTSH   =  P6 * X(1) * X(2) / P7   +   P8 * X(3)
C
C
       X(1) =  PTRH
       X(2) =  GTSH
       X(3) =  PTSH
       T    =  T  +  1
C
       IF(T.NE.MT(IT)) GOTO 100
C
       Y(1,IT)  =  PTSH
       Y(2,IT)  =   ALOG10(PTRH)
C
       K  =  IT  -  NPS  +  1
       ERS(K)  =  (Y(1,IT)  -  YA(1,IT)) * WT(1,IT)
C
       IT  =  IT  +  1
       NC  =  NC  +  1
       IF(MT(IT).NE.999.AND.NC.LT.NSIG) GOTO 100
C
C
      RETURN
      END


C=============================================================
C
C
      SUBROUTINE DIFMOD(IT,NPS,IERS,NP,P,ERS)
C     =======================================
C
C   DIFMOD RUNS MODELS WHICH REQUIRE INTEGRATION
C
C-------------------------------------------------------------
C
      DIMENSION P(10),ERS(IERS),X(10)
      COMMON /PHIL/ PR(10),Y(4,180),MT(180),YA(4,180),WT(4,180),
     1          U(180),NXX,NYY,NPD,MTYP,NSIG,DRPR(4),PT34P(4,12),IWRT
      IMPLICIT DOUBLE PRECISION (A-H,O-Z)
C
C SET INITIAL CONDITIONS BY RELAXATION FROM ZERO AT T = -100
C
      DO 10 I=1,NXX
   10   X(I) = 0.
C
      X(3)   =  0.1
C                X3 - BOUND T4 , P5 - TOTAL HORMONE
       T    =  -5
C
      NX     =  NXX
      E1     =  0.000001
      E2     =  0.000001
      DTMIN  =  0.00000001
      IF(IWRT.GE.1)WRITE(1,11) (P(I), I=1,5)
C
      TSTEP  =  0.0001
      DO 20 I = 1  , 10
       CALL INTE1(X,NX,T,TSTEP,DTMIN,E1,E2,P,IT)
       T     =  T  +  TSTEP
   20  TSTEP  = TSTEP * 2
C
  100 CONTINUE
```

```
C
   11 FORMAT(' PARS=',5F7.2)
   12 FORMAT(' XS =',2F9.5,' TIME=',F8.3,
     1       ' IT=',I3)
C
      TSTEP  =  0.1
      NSTEP  =  (MT(IT)  -  T) / TSTEP
C
      DO 150 I = 1 , NSTEP
      CALL INTE1(X,NX,T,TSTEP,DTMIN,E1,E2,P,IT)
      IF(IWRT.GE.1) WRITE(1,12) X(1),X(2),T,IT
      IF(IWRT.GE.1) WRITE(6,12) X(1),X(2),T,IT
C
  150 CONTINUE
C
      TSTEP = MT(IT)  -  T
      IF (TSTEP . GT. 0. )
     1    CALL INTE1(X,NX,T,TSTEP,DTMIN,E1,E2,P,IT)
C
C
       T         =  MT(IT)
       Y(1,IT)   =  X(2)
       Y(2,IT)   =  X(3)
C
       DO 200  I=1,NYY
            K    =  (IT - NPS)*NYY  +  I
  200   ERS(K)   =  (Y(I,IT) - YA(I,IT))*WT(I,IT)
C
       IT  =  IT  +  1
       IF(MT(IT).NE.999) GOTO 100
C
      RETURN
      END
C


C=============================================================
C
      SUBROUTINE MODEL(DX,X,TIME,NX,P,IT)
C     ===================================
C
      IMPLICIT DOUBLE PRECISION (A-H,O-Z)
      DIMENSION DX(10),X(10),P(10)
      COMMON /PHIL/ PR(10),Y(4,180),MT(180),YA(4,180),WT(4,180),
     1          U(180),NXX,NYY,NPD,MTYP,NSIG,DRPR(4),PT34P(4,12),IWRT
C
C
      IF(X(2).GT.100..OR.X(2).LT.-10..OR.X(3).GT.100.) GOTO 500
      V1    =  P(4) * X(2)
      V2    =  P(3) * X(3)
      OUTF  =  P(1) * X(2) * U(IT)
      FP    =  P(2)  -  X(3)
      IF (FP . LT . 0.) FP  = 0.
C
      DX(1)  =  OUTF
      DX(2)  = 1000*V2   -   V1 * FP    -   OUTF
      DX(3)  =  V1 * FP/1000   -   V2
C
C
      IF(IWRT.GE.1)WRITE(6,10)TIME,X(1),DX(1),X(2),DX(2),DX(3),X(3)
      IF(IWRT.EQ.2)WRITE(1,10)TIME,X(1),DX(1),X(2),DX(2),DX(3),X(3)
   10 FORMAT(' T=',F7.3,' X1=',F7.3,' D1=',F7.3,
     1 ' X2=',F7.4,' D2=',F7.4,' D3=',F7.4,' X3=',F7.4)
C
      RETURN
C
  500 DO 510 I = 1,NX
  510     DX(I)= 0.
      RETURN
      END


C=============================================================
C
C  END OF MODELS  START  OF  ERROR ANALYSIS
C
```

```
C*******************************************************
C
      SUBROUTINE PERAS(NS,NP,P,E,S,DP,FUNCT,AJAC,A1,A2,A3,A4,IDF)
C     ================
C
C
C         PARAMETER ERROR ANALYSIS - CALCULATES CONFIDENCE LIMITS ON
C         PARAMETERS ESTIMATED BY MINIMIZING SUM OF SQUARE RESIDUALS
C
C         NS     = NO OF SAMPLES (INPUT)
C         NP     = NO OF PARAMETERS (INPUT)
C         P      = NP ARRAY OF OPTIMUM PARAMETERS (INPUT)
C         E      = NS ARRAY OF MINIMIZED RESIDUALS (INPUT)
C         S      = MINIMUM SUM OF SQUARE RESIDUALS (INPUT)
C         DP     = NP ARRAY OF PARAMETER PERTURBATIONS (INPUT)
C         FUNCT  = NAME OF EXTERNAL SUBROUTINE FUNCT(NS,NP,P,E) USED TO
C                  COMPUTE RESIDUALS E FOR GIVEN PARAMETERS P
C         AJAC   = NS,NP JACOBIAN MATRIX (OUTPUT)
C         A1     = NP,NS ARRAY OF AUXILIARY STORAGE - PERAS RETURNS WITH
C                  A1 = PARAMETER SENSITIVITY MATRIX
C         A2     = NP,NP ARRAY OF AUXILIARY STORAGE - PERAS RETURNS WITH
C                  A2 = AJAC TRANSPOSE AJAC
C         A3     = NP,1 ARRAY OF AUXILIARY STORAGE - PERAS RETURNS WITH
C                  A3 = PARAMETER 95 PER CENT CONFIDENCE TOLERANCES
C         A4     = NP,NP ARRAY OF WORKING STORAGE - PERAS RETURNS WITH
C                  A4 = PARAMETER COVARIANCE MATRIX
C         W      = NS ARRAY OF AUXILIARY STORAGE - PERAS RETURNS WITH
C                  W = VARIANCE OF RESIDUALS
C
C         PERAS REQUIRES NAG SUBROUTINES F01AAF,F01CJF,F01CKF,G01BAF
C-----------------------------------------------------------------------
      DIMENSION P(10),E(NS),DP(NP),AJAC(NS,NP),A1(NP,NS),A2(NP,NP),
     1          A3(NP,1),A4(NP,NP),DUM(25),Z(1)
      COMMON /ONE/ W(5500)
      IMPLICIT DOUBLE PRECISION (A-H,O-Z)
      IF(NP.LT.2) WRITE(6,200)
  200 FORMAT(47H0*** PERAS REQUIRES AT LEAST TWO PARAMETERS ***)
      IF(NS.LE.NP) WRITE(6,201)
  201 FORMAT(40H0*** INSUFFICIENT DEGREES OF FREEDOM ***)
      IF((NP.LT.2).OR.(NS.LE.NP)) STOP
C
C     CALCULATION OF, JACOBIAN (DELTA ERR/DELTA PARAM)
C-----------------------------------------------------
      CALL JACOB(NP,P,NS,AJAC)
C
  207 FORMAT(1H ,8E15.6)
C
C         MATRIX OPERATIONS TO COMPUTE APPROXIMATE ERRORS IN PARAMETERS
C-----------------------------------------------------------------------
      IFAIL=0
      CALL F01CJF(A1,AJAC,NP,NS,0,IFAIL)
      CALL F01CKF(A2,A1,AJAC,NP,NP,NS,Z,1,1,IFAIL)
      CALL F01CKF(A3,A1,E,NP,1,NS,Z,1,1,IFAIL)
      DO 300 IC=1,NP
  300 DUM(IC)=2.0*A3(IC,1)
      WRITE(6,208) (DUM(I),I=1,NP)
  208 FORMAT(28H0ESTIMATE OF GRADIENT VECTOR//(1H ,8E15.6))
      CALL F01AAF(A2,NP,NP,A4,NP,A3,IFAIL)
      CALL F01CKF(A1,A4,A1,NP,NS,NP,A3,NP,3,IFAIL)
      WRITE(6,209)
  209 FORMAT(19H0SENSITIVITY MATRIX/)
      CALL F01CKF(A3,A1,E,NP,1,NS,Z,1,1,IFAIL)
      DO 500 IC=1,NP
  500 DUM(IC)=-A3(I,1)
      WRITE(6,210) (DUM(I),I=1,NP)
  210 FORMAT(33H0APPROXIMATE ERRORS IN PARAMETERS//(1H ,8E15.6))
      B  =  2*S/FLOAT(IDF)
      WRITE(6,211)B
  211 FORMAT(32H COVARIANCE MATRIX OF PARAMETERS,5H  B= ,F10.4/)
      DO 7 J=1,NP
      DO 510 IC=1,NP
  510 DUM(IC)=B*A4(IC,J)
    7 WRITE(6,207) (DUM(I),I=1,NP)
C
C         95 PER CENT CONFIDENCE LIMITS COMPUTED USING STUDENT T DIST.
C-----------------------------------------------------------------------
      CONFL = 0.95
```

```
      A=G01CAF(CONFL,IDF,IFAIL)
      WRITE(6,1111) A,IDF,IFAIL
 1111 FORMAT(5H  A= ,F10.4,5H IDF=,I3,6H IFAIL,I2)
      DO 8 I=1,NP
      WRITE(1,2221) B,A4(I,I)
 2221 FORMAT(5H  B =,F12.5,5H A4 =,F12.5)
    8 A3(I,1)=A*DSQRT(B*A4(I,I))
      WRITE(6,212) (A3(I,1),I=1,NP)
  212 FORMAT(48H095 PER CENT CONFIDENCE TOLERANCES ON PARAMETERS//(1H
     1       8E15.6))
C
C        RESIDUAL VARIANCES AND 95 PER CENT TOLERANCES
C-------------------------------------------------
C
C      NSIG  =  999
C      CALL JACOB(NP,P,NS,W)
CC
C      DO 11 K=1,NS
C      W(K)=0.0
C      DO 10 I=1,NP
C      D=0.0
C      DO 9 J=1,NP
C    9 D=D+AJAC(K,J)*A4(I,J)
C   10 W(K)=W(K)+D*AJAC(K,I)*B
C   11 CONTINUE
C      DO 520 IC=1,NS
C  520 E(IC)=A*DSQRT(W(IC))
C      WRITE(6,213) (W(I),E(I),I=1,NS)
C  213 FORMAT(1HO,5X,6HOUTPUT,6X,11H95 PER CENT/1H ,4X,8HVARIANCE,6X,
C     1       9HTOLERANCE//(1H ,8E12.3))
CC
C      DO 14 I=1,NP
C      DO 13 J=1,NP
C   13 A4(I,J)=B*A4(I,J)
C   14 CONTINUE
C
      RETURN
      END
C
C
      SUBROUTINE JACOB(NP,P,NS,AJAC)
C     ------------------------------
C
      DIMENSION P(10),AJAC(NS,NP),A1(2,400)
      COMMON /ONE/ W(5500)
      IMPLICIT DOUBLE PRECISION (A-H,O-Z)
C
      WRITE(6,202)
  202 FORMAT(57HOSENSITIVITY CALCULATIONS USED TO COMPUTE JACOBIAN MAT
     1X)
      WRITE(1,202)
       WRITE(1,203) NS,NP
  203 FORMAT(2I10)
      DO 4 J=1,NP
       PT   = P(J)
       DELP = PT*0.1
       P(J)=PT-DELP
       CALL FUNCT(NS,NP,P,W)
       DO 1 I=1,NS
    1     A1(1,I)=W(I)
       P(J)=PT+DELP
       CALL FUNCT(NS,NP,P,W)
       DO 2 I=1,NS
    2     A1(2,I)=W(I)
       P(J)=PT
       DO 3 I=1,NS
    3     AJAC(I,J)=0.5*(A1(2,I)-A1(1,I))/DELP
    4 CONTINUE
      WRITE(6,206)
  206 FORMAT(16HOJACOBIAN MATRIX/)
      RETURN
      END
C
C
      SUBROUTINE INTE1(X1,NXN,T1,DT,DTMIN,EREL,ERAB,PAR,IT)
C     ------------------------------------------------
```

```
C     -----------------
      IMPLICIT DOUBLE PRECISION (A-H,O-Z)
      DIMENSION X1(10),DX1(10),X1S(10),X1Z(10),OLD(10),
     1          PAR(10)
      REAL AK1(4)
      IF ( T1.EQ.0.0. AND . DT .EQ. 0.) GOTO 900
C
C
C     START
C
      DO 60 I=1,NXN
60    X1S(I)=X1(I)
      T0=T1
      N1=1
      N0=MAX0(1,N0/4)
      H=DT/FLOAT(N0)

5     DO 2 J=1,N0
       CALL MODEL(DX1,X1,T1,NXN,PAR,IT)
      DO 10 I=1,NXN
10    X1Z(I)=X1(I)
      T1=T1+0.5*H
      DO 20 I=1,NXN
      AK1(I)=DX1(I)
20       X1(I)=X1Z(I)+0.5*AK1(I)*H
       CALL MODEL(DX1,X1,T1,NXN,PAR,IT)
      DO 30 I=1,NXN
      AK1(I)=DX1(I)*2.0+AK1(I)
30    X1(I)=X1Z(I)+0.5*DX1(I)*H
       CALL MODEL(DX1,X1,T1,NXN,PAR,IT)
      DO 40 I=1,NXN
      AK1(I)=DX1(I)*2.0+AK1(I)
40    X1(I)=X1Z(I)+DX1(I)*H
      T1=T1+0.5*H
       CALL MODEL(DX1,X1,T1,NXN,PAR,IT)
      DO 2 I=1,NXN
      DX1(I)=(DX1(I)+AK1(I))/6.0
2     X1(I)=X1Z(I)+DX1(I)*H
      IF(N1.EQ.1)GO TO 3
      DO 50 I=1,NXN
      IF(ABS(OLD(I)-X1(I)).GT.(ABS(EREL*X1(I))+ERAB))GO TO 3
   50 CONTINUE
      GO TO 4
3     H=H*0.5
      IF(H.LT.DTMIN)GO TO 6
      DO 70 I=1,NXN
      OLD(I)=X1(I)
70    X1(I)=X1S(I)
      N1=0
      T1=T0
      N0=N0*2
      GO TO 5
6     WRITE(6,7)T1
      WRITE(1,7) T1
7     FORMAT(29H CONVERGENCE FAILURE AT T1 = ,F10.4)
4     RETURN
  900 CALL MODEL(DX1,X1,T1,NXN,PAR,IT)
      RETURN
      END
C
C=============================================================
C
```

Patient data from Bartlner et al used in chapter 7

Data is described in column order from the left:

1 Patient number

2 Observation number

3 Number of weeks on therapy (ends with a 999)

4 Free T4 Index result (normalised by 2.55)

5 Free T3 Index result (normalised by 31.0)

6 TSH result (normalised by 25.0)

7 Wayne index result (normalised by 4.0)

8 Serum measure not used

9 Carbimazole dosage given untill that date

The plots presented in chapter 7 show data normalised by division of this data by the factors given above. This can also be seen in the program listing in the section marked 'NORMALISE VARIABLES ...'. The factors were chosen to give an overall mean value for each variable of unity.

		T	FT4I	FT3I	TSH	CS		CARB.
1	1	0	11.6	373	0.1	22	22.3	0
1	2	1	6.1	149	0.1	22	19.3	45
1	3	2	4.1	93	0.1	18	11.2	45
1	4	3	3.0	91	4.9	12	9.2	30
1	5	4	4.7	80	31.0	14	7.1	30
1	6	5	3.5	84	92.0	7	6.2	30
1	7	9	5.6	130	52.0	6	5.5	15
1	8	12	4.5	151	27.0	4	7.1	10
1	9	16	6.6	139	22.0	4	7.6	10
		999						
2	1	0	12.8	397	0.1	31	32.8	0
2	2	1	11.2	316	0.1	31	31.7	45
2	3	2	9.0	214	1.1	31	15.6	45
2	4	3	9.0	199	0.1	28	12.2	45
2	5	4	7.6	213	0.1	23	10.9	45
2	6	5	4.6	276	1.6	18	9.8	20
2	7	9	4.2	113	7.7	10	5.7	15
2	8	12	4.1	100	26.0	4	5.8	15
2	9	16	4.2	112	53.0		5.4	10
		999						
3	1	0	17.9		0.1	31	23.4	0
3	2	1			0.1	31	27.6	45
3	3	2	7.9	250	0.1		23.4	45
3	4	3	5.0	198	0.1	21	17.7	45
3	5	4	5.7	198	0.1	16		30
3	6	5	3.8	178	0.1	17	14.7	30
3	7	8	2.9	148	0.9	16	10.5	20
3	8	8			0.1	13	14.8	20
3	9	12	11.8	548	0.1		10.8	.1
310		14	7.6	367	0.1	13	15.0	20
311		15	5.8	259	0.1	8	13.1	20
312		17	6.0	278	0.1	6	14.8	10
313		19	6.0		0.1	6	13.9	10
314		21	6.9	295	0.1	8	13.7	10
315		23	4.8	183	0.1	6		15
316		25	4.1	134	0.1	6	13.1	15
317		28	5.8	208	0.1	6	13.6	15
318		30	4.6	179	0.1	6	12.4	15
		999						

4	1	0	13.0			20	26.4	0
4	2	1	14.2	563	0.1	15		45
4	3	2	11.3	193	0.1	16		45
4	4	3	7.9	173	0.1	16	13.0	45
4	5	4	5.4	105	0.1	4	15.0	30
4	6	6	4.6			3		30
4	7	7			0.1	0	12.2	20
4	8	9	3.1	103	20.0	0	10.3	15
4	9	12	5.0	123	2.9	0	10.1	15
4	10	14	4.4	139		12	11.0	5
4	11	16	4.2	94		4	9.7	15
4	12	18	4.1	117	26.0	2	3.6	15
4	13	20	3.7	102	42.0	2	10.4	15
4	14	22	3.3	101	25.0	2	9.2	15
4	15	26	7.9	102	36.0	0	3.6	15
4	16	29	5.9	120	23.0	2	6.3	10
4	17	31	4.1	79	24.5		7.3	10
4	18	33	3.7	125	59.0	2	7.1	10
		999						
5	1	0	5.0	217	0.1	13	12.7	0
5	2	1	4.9	123	0.1	13	10.6	45
5	3	2	4.3	142	22.0	16	10.7	45
5	4	3	3.9	100	176.0	16	9.4	45
5	5	4				16	3.4	45
5	6	5	2.2	70	243.0	10		45
5	7	6	3.0	65	275.0	6	6.2	30
5	8	7	1.9	90	243.0		6.6	25
		999						
6	1	0	13.9	415	0.1	13	31.9	0
6	2	1	9.3	306	0.1	13	31.7	45
6	3	2	7.0	189	0.1	13	25.9	45
6	4	3	6.1	81	0.1	16	17.0	45
6	5	4	4.2	60	0.1	14	14.5	45
6	6	5	3.2	125	0.1	10	10.7	30
6	7	7	3.9	40	6.3		3.1	30
6	8	8	1.6	29	21.4	6	6.9	20
6	9	10	1.7	46	50.0	4	7.2	20
6	10	11	2.9	50	50.0		7.2	10
6	11	13	3.5	73	37.0	5	8.0	10
6	12	14	2.9	77	23.3	5	4.8	10
6	13	18	4.7	101	20.0	5	5.4	10
6	14	20	4.2	113	23.9	3	11.3	10
6	15	24	2.3	39	29.0	3	15.6	10
6	16	30		96	49.0	0	21.7	10
		999						
7	1	0	9.3		0.1	24		0
7	2	1	8.5	276	0.1	20	12.6	45
7	3	2	8.6	247	0.1		17.2	45
7	4	3	6.2	167	0.1	4	10.2	45
7	5	5	2.9	99	0.1	4	3.7	45
7	6	7	2.9		0.1	0		30
7	7	9	3.5	33	11.9	0	7.4	30
7	8	11	3.5	152	22.0	2	6.7	15
7	9	13	2.8	129	17.6	3	6.9	10
7	10	15	5.1	179	0.6	2	3.0	10
7	11	17	5.3	221	0.1		3.3	10
7	12	21	5.2		0.1	3	9.3	10
7	13	23	5.1	123	0.1	6	7.1	10
7	14	25		229	9.6	6	6.3	10
7	15	29	4.7		53.0	2	5.3	10
7	16	31			100.5			10
7	17	32	5.1	103	160.0	0	6.2	10
7	18	34	4.7	176	141.0	2	6.3	10
		999						
8	1	0	7.7	219	0.1	21	5.9	0
8	2	1	6.7	176	0.1	15	4.3	45
8	3	2	5.5	139	0.1	10	4.3	45
8	4	3	4.5	126	0.1	10	3.4	45
8	5	4	5.2	140	10.5	3	2.9	30
8	6	5	4.1	142	19.0		2.8	20
8	7	6	3.3	138	25.0	5	2.2	15
8	8	8	3.5	157	61.0	4	2.4	10
8	9	11	4.0	150	12.9	4	1.0	10
8	10	17	4.8	123	38.0	4	1.5	10
8	11	21	5.0	115	237.0	2	0.9	10
8	12	23			50.0	0	1.4	10
		999						
9	1	0	20.8	930	0.1	31	14.5	0
9	2	1			0.1		11.9	45
9	3	2	4.3	179	0.1	21	3.2	45
9	4	3	4.4	170	0.1	12	5.5	30
9	5	4	3.5	132	0.1		3.1	30
9	6	6			0.1	7	3.5	15
9	7	8	7.6	305	0.1			15
9	8	10	7.6	441	0.1	6		15
9	9	12	7.9	269	0.1	6		15
9	10	15	7.4	398	0.1		3.6	15
9	11	17	7.3	222	0.1	6	3.9	15
9	12	19	7.7	196	0.1	7	3.4	15
9	13	21	8.0	133	0.1	2	3.8	15
9	14	23	5.4	120	0.1	4		20
9	15	26	5.8	125	0.1	2		20
9	16	29	5.7	126	0.1	2	3.0	20
9	17	33	5.1	91	0.1	3		20
9	18	35			0.1	3		20
		999						
10		0	10.3					0
10		4	5.1			10		45
10		5	1.7			4		30
10		9	3.3	173	3.5		5.6	15
10		10	6.0			4		5
10		11			0.1		6.4	5
10		13	4.8	153	0.9	0		5
10		15	4.7			4		5
10		17				4		5
10		22		277	0.1	4	3.9	5
10		25	6.5	204		4	3.9	5
10		26	4.9		0.1	5		5
10		27				5		5
10		28				3		5
10		31	6.5		0.1			5
		999						
11	1	0	14.3	540	2.6	27	10.5	0
11	2	3				11		45
11	3	4	4.8	170	1.9			30
11	4	5				11		20
11	5	6	3.4	141	1.1	3	2.6	15
11	6	8	2.7	154	1.8	10	4.3	10
11	7	10	2.9	129	50.0			10
11	8	12	3.0	150	29.0	5	2.1	10
11	9	15	4.1	141	39.0	5	1.7	10
11	10	17	5.5	225	45.0	3	2.9	5
11	11	19	4.5	121	43.0	5	1.3	10
11	12	21	4.2	129	37.0		1.9	10
11	13	25	4.1	146	64.0	2	0.4	10
11	14	27	3.5	144	60.0	0	0.7	10
11	15	31	4.9		46.0	5	1.9	10
11	16	35	5.2	204	125.0	4	3.1	10
		999						
12	1	0	25.6	732	0.1	27	52.4	0
12	2	1	0.0		0.1	26	13.5	45
12	3	2	6.1	106	0.1	26	10.7	45
12	4	3	2.7	154	0.1	21	3.3	45
12	5	4	3.1	153	0.1	7	4.0	30
12	6	5	4.1	70	0.1		2.4	30
12	7	7			0.1	5		15
		999						

Appendix II

This appendix describes two programs written for the Apple II microcomputer in BASIC. The first was written to calculate the diffusion dependent intra-capillary free thyroxine concentration according to the model of chapter 6. The second program is an experimental implementation of the thyroidal model of chapter 7 used to describe the observed changes in T4 and T3 measures in hyperthyroid patients undergoing antithyroid drug therapy.

(1) The simulations presented in figures 6.4 to 6.7 were produced by this program. It also allows testing of the proposed diffusion depenednt delivery of T4 under a range of conditions. For demonstration purposes the grapics screen is used by plotting a normalised intra-capillary concentration over a pre-drawn set of axsis and scales. The normalisation and the pre-drawn scales reduce the complexity of the programming and avoid the problems of mixing graphics and text on this machine. The intra-capillary concentration is therefore allways expressed in terms of the in vitro (no hormone loss) equilibrium free hormone concentration. Results are plotted from the centre to the capillary wall and again the distance from the capillary axis is expressed in terms of the capillary radius giving a fixed 0 to 1 scale. As the plot of the intra-capillary concentration is being plotted the actual values are being plotted out for subsequent reference. The user may change any of the parameters and/or clear the screen if required. 'Input' to the system is the loss of hormone through the capillary wall. This may be set either as an actual flow rate, when the apparent extra-capillary hormone concentration will be calculated, or as the extra-capillary concentration, whereupon the flow rate will be calculated.

Calcuation of the free hormone concentration profile requires the evaluation of two Bessel series of order zero and one. This is acheived by the subroutines at lines 2000 and 3000 respectivly. If either summation fails a warning flag appears. The "BLOAD S" instruction reloads the background scales and axsis so clearing the graphics screen.

The next two pages give the BASIC listing of the program

```
40  READ N0,N1,N2,T0,NH,NT
50  DATA  0,1,2,10,100,1000
60  READ P(1),P(2),P(3),P(4)
70  DATA  0,6.5E-2,8E-4,3E-4
80  READ P(5),P(6),P(7),P(8),P(9)
90  DATA  4.09E4,1.06,0.1,0.1,2.5E-5
95 P(9) =  - 1
100 D$ =  CHR$ (4)
110  REM  SPACE FOR DSC&SCALES
120  HGR
130  POKE  - 16302,0
140  PRINT D$"BLOAD S"
150  TEXT : HOME
200 YH = 160
205 YL = 22
210 XH = 255
215 XL = 40
220 NC = T0
230 XM = (XH - XL) / NC
400  POKE  - 16302,0
420  HCOLOR= 3
500  POKE  - 16303,0
505  PRINT
510  PRINT "CI="P(1);"  KP="P(2);"  RC="P(3)
520  PRINT "D=";P(4);"  AC="P(5);"  DC="P(6)
530  PRINT "PRF="P(7);"  HB="P(8);"  LOSS="P(9)
535  PRINT
540  INPUT "PAR. NO.?";IP
545  PRINT
550  IF IP > N0 THEN  INPUT "PAR. VALUE ?";P(IP): GOTO 510
580 CI = P(1):KP = P(2)
590 RC = P(3):D = P(4)
600 KA = P(5) * P(7)
610 KD = P(6) * P(8)
620 EQ = KD / KA
630 LA =  SQR (KA / D)
640  PRINT "EQ=";EQ
650  PRINT "KD=";KD;"KA=";KA
660  PRINT "LA=";LA
670 FL = P(9)
700 X = LA * RC
710  GOSUB 2000
720  GOSUB 3000
725  IF FL >  = N0 THEN CI = EQ - FL * I0 / (D * LA * I1) - FL / KP
730 Y = LA * D * I1 / KP + I0
740 Z = (EQ - CI) / Y
745 SL = (YH - YL) / EQ
780  POKE  - 16304,0
790  POKE  - 16297,0
```

```
795  PRINT : PRINT "RADIUS                CONC.": PRINT
800  FOR IL = N0 TO NC
810 R = IL * RC / NC
820 X = LA * R: GOSUB 2000
830 C = EQ - Z * I0
835  PRINT R,C
840 RP = XL + XM * IL
850  IF C < N0 THEN C = N0
860 CP = YH - SL * C
870  IF CP < N0 THEN CP = N0
880  IF IL > N0 THEN  HPLOT RO,CO TO RP,CP
890 RO = RP:CO = CP
900  NEXT IL
905 CC = CI: IF CC < N0 THEN CC = N0
910 RP = RP + T0:CP = YH - SL * CC
913  IF CP < N0 THEN CP = N0
917  HPLOT  TO RP,CP
920 RP = RP + T0: HPLOT  TO RP,CP
930  IF FL < N0 THEN  PRINT : PRINT "LOSS RATE=";KP * (C - CI)
940  IF FL >  = N0 THEN  PRINT : PRINT "FIXED LOSS, CI=";CI
960  PRINT : PRINT " EQ="EQ
970  GET C$
980  IF C$ = "C" THEN 100
990  IF C$ <  > "E" THEN  GOTO 500
1111  END
1900  REM  BF I0 TEST
1910 N0 = 0:N1 = 1:NT = 1000:N2 = 2
1920  FOR II = 1 TO 100:X = II / 10
2000 ER = X / NT:I0 = N0:N = N1
2005  IF X = N0 THEN I0 = N1: RETURN
2010  FOR I = N2 TO NT STEP N2
2020 I0 = I0 + N
2030 V = X / I:N = N * V * V
2040  IF N < ER THEN 2100
2050  NEXT I
2070  PRINT "I0 FAIL<<<"
2080  PRINT "X=";X;"I0=";I0
2100  RETURN
2900  REM  I1 TESTER
2910 N0 = 0:N1 = 1:N2 = 2:NH = 100:NT = 1000
2920  FOR II = 1 TO 100
2930 X = II / 10
3000  IF X > 90 THEN  PRINT "ARG TOO BIG": GOTO 3090
3010 N = N1:I1 = N0:ER = X / NT
3020  FOR I = N2 TO NT STEP N2
3030 V = X / I:N = N * V
3040 I1 = I1 + N:N = N * V
3050  IF N < ER THEN  RETURN
3060  NEXT I
3090  PRINT "I1 FAILS<<<<<"
3095  PRINT "X=";X;"I1=";I1
3100  END
```

(2) Simulation of thyroidal response to antithyroid drugs. This program consists of two parts. The first is used to load, edit, and save patient data files. The second allows simulation of the thyroidal response by model parameters supplied by the user or after optimisation on the data itself. As only the thyroidal component has been included the input data is restricted to the T4, and T3 measures and the Carbimazole drug dosage.

The first program (listed on the next two pages) is simply used for the generation of the patient data files subsequently read by the simulation and optimisation program. The strings defined in lines 4 and 5 are written to the data file to appear as program prompts. This allows a more general application of the fitter program and saves some memory space. As APPLESOFT lacks a 'print using' function the routine at line 100 in both programs is used to format the output at the cost of a small delay. The particular routine required is selected on line 30 after the reply to the menu printed by line 20. Note that as both of these programs are versions of a more general curve-fitting program a number of lines are redundant. The data input program is listed on the next two pages.

Program PAT.FIT requires a special routine to allow text to be added to the graphics screen and it is switched in and out by lines 5050 and 5260 respectivly. Data files are read and the data may be edited by the routines from 8200 onwards. The thyroidal model appears between lines 20 and 70 and is located near the 'top' of the code to reduce interpreter search delays. Lines 200 to 520 call the routines to load data, edit and present it on the text and graphics screens as shown in figures 7.52 and 7.53. The user may adjust the model parameters manually and observe the resulting model response or go directly to the optimisation routine. A simplex algorithm (530 to 650) calls additional routines as required (1000 to 1190). Two routines from 1200 and 1300 onwards update the whole set of data on the text screen or only the model output. The search routine may be interupted at any time and will terminate after 300 iterations or when improvements in the residual error become insignificant. At termination the final fit will be plotted and the user asked if the fit is O.K. When a prompt with a yes/no reply appears the user may clear the graphics screen (press s), plot the current model response (p) or produce a hard copy of the graphics screen (h). The full listing appears on pages 197 to 198.

```
1  REM  !  X$7000 ,L$7000,S$9000
2  DIM S1(20),R2(20,2),U(20),S$(15)
3 N1 = 1:N2 = 2:N3 = 3:N4 = 4:N5 = 5:NH = 100:NM = 1E - 3:T0 = 10:O
     1 = .1:05 = .5:FT = 50:NU = 1E20:DP = 1:NP = 2:NS = 3
4 OP$ = "PR#1":D$ =  CHR$ (4):A$ = "B":S$(7) = "ITERATION NO.    !ER
     ROR=                    ======================================
     PARAM 1 ! PARAM 2 ! PARAM 3 ! PARAM 4"
5 S$(0) = "PLOT F/B":S$(1) = "PLOT LINEAR DOSE":S$(2) = "ANY CORREC
     TIONS":S$(3) = "WEIGHTED FIT":S$(4) = "FIT O.K.":S$(5) = "PATI
     ENTS CLINICAL DATA":S$(6) = "MANUAL INPUT OF INITIAL PARAMETER
     S"
6 NN = 3:S0 = 1:BK = 10:NW = 5:SW = .5:SP% = 155:PU = 10:TM = 50000
     :NP = 2:NS = 3
20  HOME : PRINT : PRINT " 1 INPUT PAT. DATA": PRINT " 2 EDIT PAT.
     DATA": PRINT " 3 LOAD DATA FILE": PRINT " 4 SAVE DATA FILE": PRINT
     " 5 BLOAD BINARY LIB."
25  GET C$:V =  VAL (C$)
30  ON V GOSUB 1000,8200,8600,8000,8500,8200
40  GOTO 20
100  PRINT  RIGHT$ ( LEFT$ ("       -",6 -  SGN (V)) +  STR$ ( INT (
      ABS (V) + 05 / PU)) + "." +  RIGHT$ ( STR$ ( INT (( ABS (V) +
     NH) * PU + 05)),DP),NW);:X =  FRE (0): RETURN
1000  HOME : PRINT " INPUT PATIENT DATA": PRINT : GOSUB 7300
1010  PRINT
1020  PRINT " INPUT NO. OF MEASUREMENT TIMES ";: INPUT S9:S8 = S9 -
     1
1025  PRINT
1030  PRINT " INPUT NO. OF MEAS.";: INPUT S0
1040  HOME : PRINT "INPUT TIME,DOSE & RESULTS IN ORDER"
1050  FOR I = 0 TO S8: INPUT TM(I),R2(I,0),R2(I,1),R2(I,2): NEXT I
1070 S1(I) =  - 999
1080  PRINT : PRINT "ERROR IN MEAS.(2 NO.S)";: INPUT A0,A1
1090  RETURN
7000  PRINT : PRINT "ANY CORRECTIONS";
7010  GET C$: IF C$ <  > "Y" AND C$ <  > "N" THEN 7010
7020  PRINT C$: RETURN
7030  VTAB 19: HTAB 1: RETURN
7300  PRINT "INPUT PAT. NAME";: INPUT N$: RETURN
```

```
8000 F$ = "PATIENT " + N$ + " DATA"
8005  PRINT : PRINT D$"OPEN"F$: PRINT D$"WRITE"F$
8010  FOR I = 0 TO 9: PRINT S$(I): NEXT
8020  PRINT N$: PRINT OP$
8040  PRINT S0: PRINT S9: PRINT NP
8050  FOR I = 0 TO S8: PRINT TM(I)
8060  FOR J = 0 TO S0: PRINT R2(I,J): NEXT J
8070  NEXT I
8080  FOR I = 1 TO 4: PRINT P(I): NEXT
8090  PRINT D$"CLOSE": RETURN
8200 NW = 5:PU = 10:YL = NH:YH = 0:NN = S8: HOME : HTAB 10: PRINT S
     $(5)
8210  PRINT "PATIENT "N$" "A$" DATA OVER TIME": PRINT "N  TIME DOSE
      ";: FOR I = 1 TO S0: PRINT  SPC( 4);I;: NEXT : PRINT
8220  FOR I = 0 TO NN:V1 = N0:V2 = N0: PRINT I + 1; TAB( 4);TM(I); TAB(
     9)
8230  FOR J = 0 TO S0:V = R2(I,J): IF V > 0 THEN V1 = V1 + N1:V2 =
     V2 + V: IF V < YL THEN YL = V:V4 = I
8240  GOSUB 100: IF V > YH THEN YH = V:V5 = I
8250  NEXT J
8360  PRINT : NEXT I
8370  GOSUB 7000: IF C$ = "N" THEN  RETURN
8380  GOSUB 7030: PRINT "OBSERVATION NO.";: INPUT C$:V1 =  VAL (C$)
      - 1: IF V1 < 0 OR V1 > NN THEN 8380
8390  VTAB 19: HTAB 20: PRINT "MEASURE NO.";: INPUT C$:V2 =  VAL (C
     $): IF V2 < 0 OR V2 > S0 THEN 8390
8400  VTAB 23: HTAB 1: PRINT "OLD VALUE=";R2(V1,V2);: HTAB 20: PRINT
     "NEW VALUE=";: INPUT C$:V =  VAL (C$): IF V < 0 OR V > 100 THEN
     8400
8410 R2(V1,V2) = V: GOTO 8200
8450  FOR I = 0 TO NN:W(I) = XT(0,I) / S0: IF C$ = "Y" THEN W(I) =
     W(I) / XT(2,I)
8460  NEXT I: RETURN
8500  PRINT "";E = NU: POP : RETURN
8600  HOME : PRINT "READ DATA FILE": PRINT : GOSUB 7300
8605  PRINT : PRINT D$"READ PATIENT ";N$;" DATA"
8610  FOR I = 0 TO 9: INPUT S$(I): NEXT I
8612  INPUT N$: INPUT OP$
8614  INPUT S0: INPUT S9: INPUT NP
8616 S8 = S9 - 1
8620  FOR I = 0 TO S8: INPUT TM(I)
8622  FOR J = 0 TO S0: INPUT R2(I,J): NEXT J
8624  NEXT I
8630  FOR I = 1 TO NP: INPUT P(I): NEXT : PRINT : PRINT D$"CLOSE": RETURN
```

```
1  LOMEM: 28700
2  DIM P(4),XT(2,10),R2(10,3),E(5),PR(4,5),Y(10),YH(10),S$(9),TM(10)
3 N1 = 1:N2 = 2:NH = 100:NM = 1E - 4:T0 = 10:01 = .1:05 = .5:FT = 50:NU =
    1E20:DP = 1:NP = 4:NS = 3:D$ =  CHR$ (4)
5  GOTO 200
20 P1 = P(1) * 10:P2 = P(2):P3 = P(3):P4 = P(4)
21  IF  ABS (1 - P2) < NM THEN E = NU: RETURN
25 X(1) = P1 / (1 - P2):X(2) = P3 * X(1)
26  IF PT THEN  GOSUB 7100
30 UIN = R2(0,0):E = 0:IT = 0
45  FOR T =  - 1 TO XH
50 Y(1) = P1 *  EXP ( - P4 * UIN) + P2 * X(1)
55 Y(2) = P3 * Y(1)
60  IF PT THEN  GOSUB 80
65  IF T = TM(IT) THEN  GOSUB 90:IT = IT + 1:UIN = R2(IT,0)
70 X(1) = Y(1):X(2) = Y(2): NEXT T: GOSUB 1220: RETURN
80  FOR I = 1 TO S0: IF X(I) < YH AND X(I) > YL AND Y(I) < YH AND Y(I) >
    YL AND T > 0 AND T < XH THEN  HPLOT  FN XP(T), FN YP(X(I)) TO  FN X
    P(T + N1), FN YP(Y(I))
85  NEXT I: RETURN
90  FOR I = 1 TO S0:V = (X(I) - R2(IT,I)) * WT(IT,I):E = E + V * V: IF W
    R THEN RS(IT,I) = X(I)
95  NEXT I: RETURN
100  PRINT  RIGHT$ ( LEFT$ ("       -",6 -  SGN (V)) +  STR$ ( INT ( ABS
    (V) + 05 / PU)) + "." +  RIGHT$ ( STR$ ( INT (( ABS (V) + NH) * PU +
    05)),DP),NW);: RETURN
200  HOME : PRINT " THYROID PATIENT DATA PROGRAM"
210  GOSUB 7300: GOSUB 8600
220  DEF  FN N(V) =  INT (PU * V + 05) / PU: DEF  FN R(V) = V *  NOT PY +
    PY * (NH - V) / V
230  DEF  FN XP(V) = X1 * V + X2: DEF  FN YP(V) = Y1 * V + Y2
250  GOSUB 8200
300  GOSUB 7030: PRINT "NO. OF FITTED PARAMETERS ";: INPUT C$:NP =  VAL
    (C$): IF NP < 1 OR NP > 4 THEN 300
301 NS = NP + 1
310  GOSUB 8450
370  GOSUB 1300: VTAB 21: HTAB 1: PRINT S$(7);: IF P(1) <  > 0 THEN 520
500 IO = 6: GOSUB 7000: IF C$ = "N" THEN P(1) = .2:P(2) = .8:P(3) = .95:
    P(4) = 0.1: GOTO 520
510  GOSUB 7030: PRINT "PAR'S";: FOR I = 1 TO 4: VTAB 19: HTAB I * 8: PRINT
    I;: INPUT C$:P(I) =  VAL (C$): NEXT
520 PT = 1: GOSUB 1200:PT = 0:IO = 2: GOSUB 7000: IF C$ = "Y" THEN 500
540  FOR I = 1 TO NP:V = P(I): FOR J = 1 TO NS:PR(I,J) = V + (I = J) * V
     * 01: NEXT : NEXT :S = 0: GOSUB 1180
550  FOR IK = 1 TO 300:B = 0:S = 0: GOSUB 1010:B = I2:S = I1: GOSUB 1010
    :M = I1
560 V = (E(B) - E(S)) / E(B): IF  PEEK ( - 16384) = 155 OR IK = 300 OR (
    IK > NH AND V < 01) OR V < NM THEN IK = 300: NEXT : GOTO 2000
570  VTAB 21: HTAB 15: PRINT IK;: GOSUB 1060: IF  PEEK ( - 16384) = 197 THEN
     GOSUB 1200
580  FOR I = 1 TO NP:P(I) = PR(I,N0) - N2 * PR(I,B): NEXT I: GOSUB 20
590  IF E =  < E(S) THEN  GOSUB 1100: NEXT IK
600  IF E =  < E(B) THEN  GOSUB 1000
610  IF E =  < E(M) THEN  NEXT IK
620  IF E =  < E(B) THEN  GOSUB 1080
630  FOR I = 1 TO NP:P(I) = .25 * (PR(I,N0) + PR(I,B)): NEXT I
640  GOSUB 20: IF E =  < E(S) THEN  GOSUB 1040: NEXT IK
650  FOR J = 1 TO NS: FOR I = 1 TO NP:PR(I,J) = .25 * (PR(I,J) + PR(I,S))
    : NEXT : NEXT : GOSUB 1180: NEXT IK
```

```
1000  FOR I = 1 TO NP:PR(I,B) = P(I): NEXT :E(B) = E: RETURN : REM
      SAVE<<
1010 V1 = N[illegible]: [illegible] = N0
1020  FOR I = 1 TO NS: IF I = B OR I = S THEN  NEXT : RETURN
1030 V = E(I): IF V < V1 THEN V1 = V:I1 = I
1040  IF V > V2 THEN V2 = V:I2 = I
1050  NEXT : RETURN : REM   SORT<<
1080  FOR I = 1 TO NP:V = N0: FOR J = N1 TO NS:V = V + PR(I,J): NEXT
     :PR(I,N0) = V: NEXT : RETURN : REM    SUM<<
1100  FOR I = 1 TO NP:V = 1.5 * PR(I,N0) - 3.5 * PR(I,B):PR(I,B) = P(
     I):P(I) = V: NEXT :E(B) = E: GOSUB 20: IF E > E(S) THEN  RETURN

1110  GOSUB 1000: RETURN : REM   BETTER<<
1150 NY = 0:Y1 = 0
1160  FOR I = 0 TO NN: IF W(I) > N0 THEN Y1 = Y1 + Y(I) * W(I):NY = N
     Y + W(I)
1170  NEXT I:Y1 = Y1 / NY: RETURN
1180  FOR J = 1 TO NS: IF J <  > S THEN  FOR I = 1 TO NP:P(I) = PR(I,
     J): NEXT : GOSUB 20:E(J) = E
1190  NEXT J: RETURN
1200 WR = 1: GOSUB 20:WR = 0
1210  FOR I = 0 TO S0: FOR J = 1 TO S0: GOSUB 1250: NEXT J: NEXT I
1220 V = E:NW = 9:DP = 2:PU = NH: VTAB 21: HTAB 29: GOSUB 100
1230  VTAB 24: HTAB 1: FOR I = 1 TO 3:V = P(I): GOSUB 100: PRINT " ";
     : NEXT :V = P(1): GOSUB 100:NW = 5:DP = 1:PU = 10: RETURN
1250 V = RS(I,J): VTAB 3 + I: HTAB (14 * J + 5): GOSUB 100: RETURN
1300  HOME : HTAB 5: PRINT S$(5): PRINT "TIME DOSE  MEA.1  CAL.1  MEA
     .2  CAL.2"
1310  FOR I = 0 TO NN: CALL  - 868: PRINT TM(I);: HTAB 5:V = R2(I,0):
      GOSUB 100: FOR J = 1 TO S0:V = R2(I,J): HTAB (J * 14 - 2): GOSUB
     100: GOSUB 1250: NEXT J
1320  PRINT : NEXT : RETURN
2000  FOR I = 1 TO NP:P(I) = PR(I,S): NEXT I
2100 PT = 1: GOSUB 1200:PT = 0:IO = 4: GOSUB 7000: IF C$ = "N" THEN 3
     00
2110  RUN 1
4000  END
5000 PY = 0:PX = 0: REM FIXED SCALES
5010 XH = 34:V =  - 1:XL = V:X2 = PX * XL
5020 X1 = 254 / (XH - X2):X2 = 20 - X1 * X2
5030 YL = 0:YH = 20:Y1 = 175 / (YL - YH):Y2 = 180 - Y1 * YL: RETURN
5050  HGR : POKE  - 16302,0: PR# 0: IN# 0: POKE 54,0: POKE 55,103: HCOLOR=
     3
5060  VTAB 1: HTAB 1: PRINT " PATIENT "N$" RESULTS VS TIME (WEEKS)";
5070  FOR I = 0 TO NH STEP 5: IF I >  = YL AND I < YH THEN V =  FN YP
     (I): HTAB 1: VTAB  INT (O5 + 23 * V / 180): PRINT I;: HPLOT 20,V
      TO 274,V
5080  NEXT I:V =  - 3: IF PX THEN V1 = T0 ^ ( INT ( LOG (XH) /  LOG (
     T0) + O5) - 1)
5090  FOR V = 0 TO XH STEP 5: IF V < XL THEN 5100
5097 XP =  FN XP(V): VTAB 24: HTAB  INT (40 * XP / 270): PRINT V;: HPLOT
     XP,T0 TO XP,180
5100  NEXT V:V = XL
5110  REM XP =  FN XP(V): HPLOT XP,1 TO XP,180:YP =  FN YP(YL): HPLOT
      20,YP TO 279,YP
5210  FOR I = 0 TO NN:XP =  FN XP(TM(I))
5220  FOR J = 1 TO S0:V = R2(I,J): IF V >  = YL THEN V =  FN YP(V): HPLOT
     XP - 3,V TO XP + 3,V: HPLOT XP,V - 3 TO XP,V + 3
5230  NEXT J
5250  NEXT I
5260  POKE 54,189: POKE 55,158: RETURN
```

```
7000  GOSUB 7030: PRINT S$(IO)" Y/N ";
7010  VTAB 19: GET C$: IF C$ = "N" OR C$ = "Y" THEN  TEXT : RETURN
7020  IF C$ =  CHR$ (27) THEN  GOSUB,7100
7021  IF C$ =  CHR$ (32) THEN  TEXT
7022  IF IO < 2 THEN 7000
7023  IF C$ = "S" THEN  GOSUB 5000: GOSUB 5050
7025  IF C$ = "P" THEN  GOSUB 7100:PT = 1: GOSUB 1200:PT = 0
7026  IF C$ = "H" THEN  CALL  - 16039
7027  IF C$ = "L" THEN  CALL  - 16015
7028  GOTO 7000
7030  VTAB 19: HTAB 1: CALL  - 868: RETURN
7100  POKE  - 16304,0: RETURN

8200 NN = 5:PU = 10:YL = NH:YH = 0: HOME : HTAB 10: PRINT S$(5);NN =
     S8
8210  PRINT "PATIENT "N$" DATA OVER TIME": PRINT "N  TIME  DOSE";: FOR
     I = 1 TO S0: PRINT  SPC( 4);I;: NEXT I: PRINT
8220  FOR I = 0 TO NN:V1 = N0:V2 = N0: PRINT I + 1; TAB( 4);TM(I); TAB(
     9)
8230  FOR J = 0 TO S0:V = R2(I,J): IF V > 0 THEN V1 = V1 + N1:V2 = V2
     + V: IF V < YL THEN YL = V:V4 = I
8240  GOSUB 100: IF V > YH AND J > 0 THEN YH = V:V5 = I
8250  NEXT J:V = N0: IF V1 > N0 THEN V = V2 / V1
8260  PRINT : NEXT I
8270 XP(0,2) = YH:XP(1,1) = YH:XP(0,1) = YL:XP(1,2) = YL: PRINT D$"PR
     #0": GOSUB 5010: GOSUB 5050: IF P(1) <  > 0 THEN  GOSUB 5300
8275 IO = 2: GOSUB 7000: IF C$ = "N" THEN  RETURN
8280  GOSUB 7030: PRINT "OBSERVATION NO.";: INPUT C$:V1 =  VAL (C$) -
     1: IF V1 < 0 OR V1 > NN THEN 8280
8290  VTAB 19: HTAB 20: PRINT "MEASUREMENT NO.";: INPUT C$:V2 =  VAL
     (C$): IF V2 < 0 OR V2 > S0 THEN 8290
8400  VTAB 23: HTAB 1: PRINT "OLD VALUE="; FN N(R2(V1,V2));: HTAB 20:
      PRINT "NEW VALUE=";: INPUT C$:V =  VAL (C$): IF V < 0 OR V > 10
     0 THEN 8400
8410 R2(V1,V2) = V: GOTO 8200
8450  FOR I = 0 TO S8: FOR J = 1 TO S0:WT(I,J) = (R2(I,J) > 0): NEXT
     J: NEXT I: RETURN
8500  PRINT "";E = NU: POP : RETURN
8600  PRINT : PRINT D$"READ PATIENT "N$" DATA
8610  FOR I = 0 TO 9: INPUT S$(I): NEXT I
8612  INPUT N$: INPUT OP$
8614  INPUT S0: INPUT S9: INPUT NP
8616 S8 = S9 - 1
8620  FOR I = 0 TO S8: INPUT TM(I)
8622  FOR J = 0 TO S0: INPUT R2(I,J): NEXT J
8624  NEXT I
8630  FOR I = 1 TO NP: INPUT P(I): NEXT : PRINT : PRINT D$"CLOSE": RETURN

9999  END : REM  END OF PROGRAM
```