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THE RELATIONSHIP BETWEEN CHANGES IN CRITICALLY ILL SEPTIC AND NON SEPTIC PATIENTS AND CIRCULATING THYROXINE LEVELS.

Gavin John Churchyard.

A dissertation submitted to the Faculty of Medicine, University of the Witwatersrand, Johannesburg, in part fulfilment of the requirements for the degree Master of Medicine in Internal Medicine. 1993.

Welkom, 1993

ABSTRACT.

Normal thyroid physiology and pathophysiology with reference to non-thyroidal illness is reviewed, including infections, specific disease states and drugs and their effects on thyroid function tests.

A review of the literature reveals that following almost any infection the serum T4 and T3 decrease as a result of diminished secretion of TSH and thyroxine, accelerated T4 disappearance, inhibition of hormone binding to transport proteins and decreased peripheral T4 to T3 conversion.

This study evaluates (i) the severity of the euthyroid sick syndrome at presentation in critically ill septic and non septic patients, and (ii) the relationship between changes in circulating thyroxine levels and clinical progress, and (iii) the relationship between serum thyroxine, APACHE II score and outcome. The use of serum thyroxine levels as a prognostic indicator is discussed.

Adult Patients admitted to the Baragwanath Hospital Intensive Care Unit at presentation were divided into non septic (n=15), septic syndrome (n=25) and septic shock (n=8) groups. Total thyroxine (TT4), total triiodothyronine (TT3), thyroxine binding globulin (TBG), thyrotropin (TSH) and APACHE II score were determined on admission and TT4 was measured serially in the septic syndrome group. A group of euthyroid blood donors were used as controls.

A significant reduction in mean TT4, TT3 and TBG at presentation was demonstrated between the non septic, septic syndrome and septic shock groups. As the severity of illness increased due to sepsis, so to did the mortality and the perturbations in thyroid hormone economy. A relationship between TT4, APACHE II score and outcome was demonstrated. A nadir TT4 of less than 35nmol/L was found to have a predictive accuracy for outcome of 78%. The usefulness of TT4 as a "bedside" prognostic indicator is questioned.

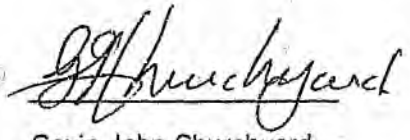
Dedication.

This thesis is dedicated to my wife and children for their long suffering, patience and surport during the writing of this thesis.

Declaration.

I declare that this dissertation is my own work and that it has not been submitted for any other degree in any other university.

This study has been approved by the Committee for Research on Human Subjects, University of the Witwatersrand, Johannesburg, Protocol No. 29/2/91.



Gavin John Churchyard

28th day of September 1993.

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I wish to thank the following individuals who made this work possible:

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Parts of this study have been published in abstract form at the following congresses.

1. The South African Metabolic, Diabetes and Endocrine society (1992).
2. The South African society of Anaesthesiology (1992).
3. The 1992 Critical Care and Emergency Medicine Congress, Brussels.

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List of Abreviations.

T4.	Thyroxine
TT4.	Total thyroxine
%FT4 D	Percentage free fraction by equilibrium dialysis
Absolute FT4 D	Absolute free T4 by dialysis
T3.	Triiodothyronine
TT3	Total triiodothyronine
rT3	reverse triiodothyronine
Tg	Thyroglobulin
MIT	Monoiodotyrosine
DIT	Diiodotyrosine
FTI	Free thyroxine illness
TSH	Thyroid Simulating Hormone (Thyrotropin)
TRH	Thyrotropin releasing hormone
TBP	Thyroid hormone binding proteins
TBG	Thyroxine binding globulin
TBPA	Thyroxine binding prealbumin
FT4D	Free thyroxine by equilibrium dialysis
RAIU	Radioactive iodine uptake
T3RU	T3 resin uptake
TFT's	Thyroid function tests
NTI	Nonthyroidal illness
FSH	Follicle stimulating hormone
LH	Lutenising hormone
HCG	Human chorionic gonadotrophin
cAMP	Cyclic Adenosine MonoPhosphate
TNF-α	Tumor necrosis factor-alpha
PAF	Platelet activating factor
IL	Interleukin
GM-CSF	Granulocyte monocyte colony stimulating factor
T cell	Thymic derived lymphocyte
EDRF	Endothelial-derived relaxing factor
MOF	Multiple organ failure
SIRS	Systemic inflammatory response syndrome
ARDS	Adult respiratory syndrome
Fio_2	Inspired oxygen concentration
P	Partial pressure
A	Alveolar
a	arteriolar
O_2	Oxygen
APACHE	Acute Physiology and Chronic Health Evaluation

P CONC.	Plasma concentration
mRNA	Messenger ribonuclear acid
tRNA	Transfer ribonuclear acid
m	Mili (10^{-3})
μ	Micro (10^{-6})
n	Nano (10^{-9})
g	gram
K	Kilo
dl	decaiitre
L	Litre
IU	International units
mol	Mole (molecular weight * mass)
n	number of samples
SD	Standard deviation
R	Coefficient of correlation
P	probability coefficient of significance
CV	Coefficients of variation
*	multiplication
α-GPD	alpha-glycerophosphate dehydrogenase
RIA	Radioimmunoassay
IRMA	Immunoradiometric assay
Hg	Mercury
Hr	Hour
N/S	Non septic
S/Syn	Septic syndrome
S/S	Septic shock
CRF	Chronic renal failure
ARF	Acute renal failure
H/T	Hypertesion
NIDDM	Non insulin dependant diabetes melitus
CMO	Cardiomyopathy
DU	uodenal ulcer
Comm. Pneumonia	Community aquired pneumonia
Hosp. Pneumonia	Hospital aquired pneumonia
vs	versus
E.S.S	Euthyroid Sick Syndrome
ALB	Albumin

1) ENDOCRINOLOGY:

1.1 Synthesis and Secretion of the Thyroid Hormones.

The thyroid gland is responsible for producing thyroxine (T4), triiodothyronine (T3) and reverse triiodothyronine (rT3).

The main biosynthetic phases are 1) trapping of iodide, 2) conversion to an activated form, 3) iodination of tyrosine with in thyroglobulin (Tg), ie, organification, 4) "coupling" of the resultant monoiodotyrosines (MIT) and diiodotyrosines (DIT) to form T3 and T4, 5) the uptake and hydrolysis of thyroglobulin and subsequent release and secretion of thyroid hormones into the circulation (fig 1 & 2)(1). Thyroid stimulating hormone (TSH) stimulates both the biosynthesis and secretion of thyroid hormones, via the adenylate cyclase system (1). The thyroid is the only source of T4, however 80% of circulating T3 is derived from peripheral deiodination of T4 (fig 3)(2). Triiodothyronine is responsible for most of the action of the thyroid hormones (3,4).

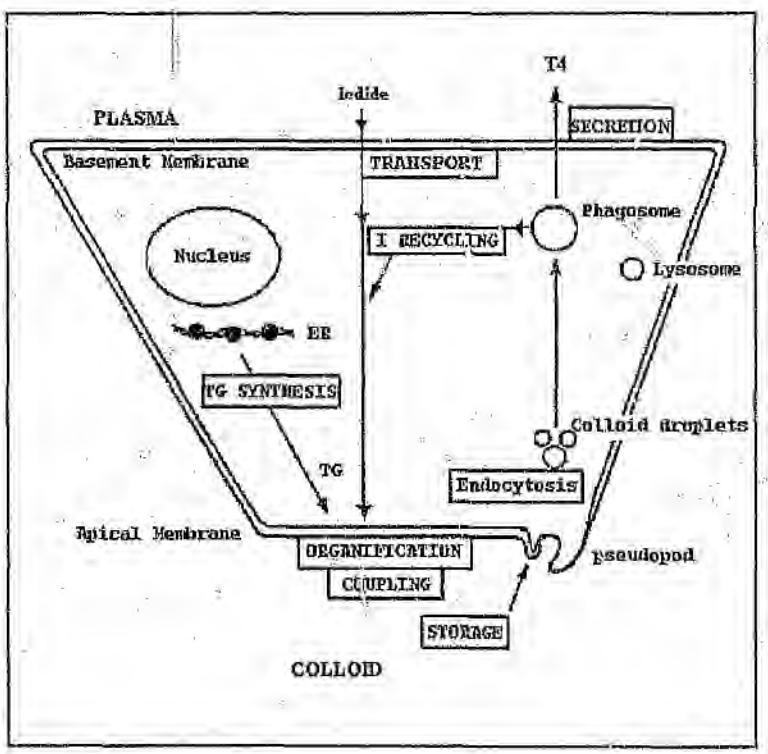


Fig. 1. Thyroid hormone synthesis. Iodide is transported from the plasma, through the cell, to the apical membrane, where it is organified to TG synthesized within the thyroid cell. Hormone stored as colloid re-enters the cell through endocytosis and moves back toward the basal membrane where T4 is secreted. Nonhormonal iodide is recycled.

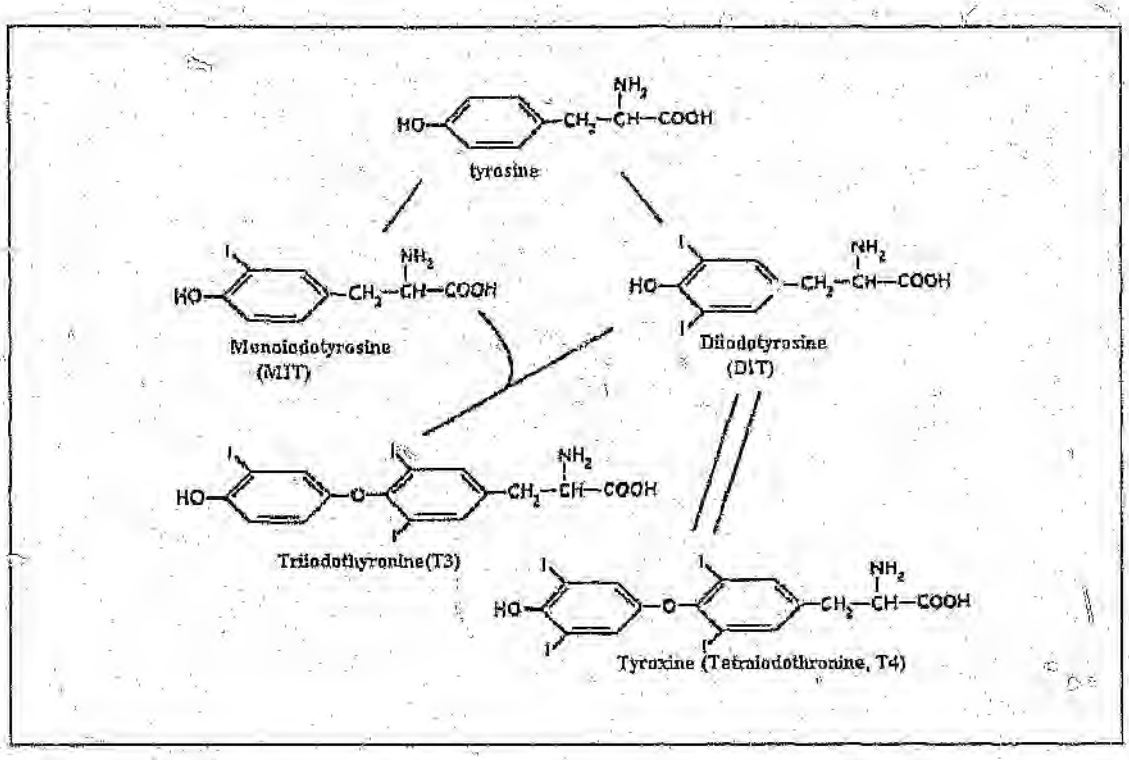


Fig 2. Scheme of coupling reactions. After tyrosine is iodinated to form MIT or DIT (organification of the iodine), MIT and DIT combine to form T3, or two molecules of DIT form T4.

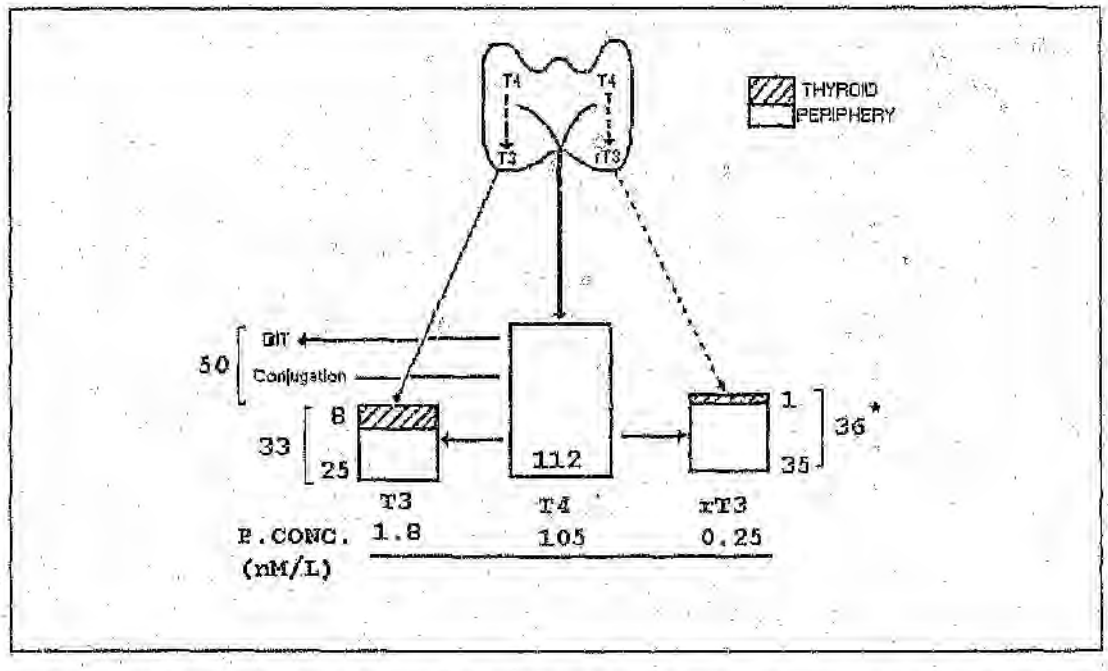


Fig3. Schematic representation of production of T4, T3, and rT3 and of nondeiodinative metabolism of T4. Plasma concentration (P. CONC) in nanomoles/liter; other figures (*) indicate daily production rates (in nanomoles) in normal humans.

1.2 Regulation of Thyroid Hormone Secretion.

Schema of the hypothalamic-pituitary-thyroid axis and its hormonal control (Fig 4)(5).

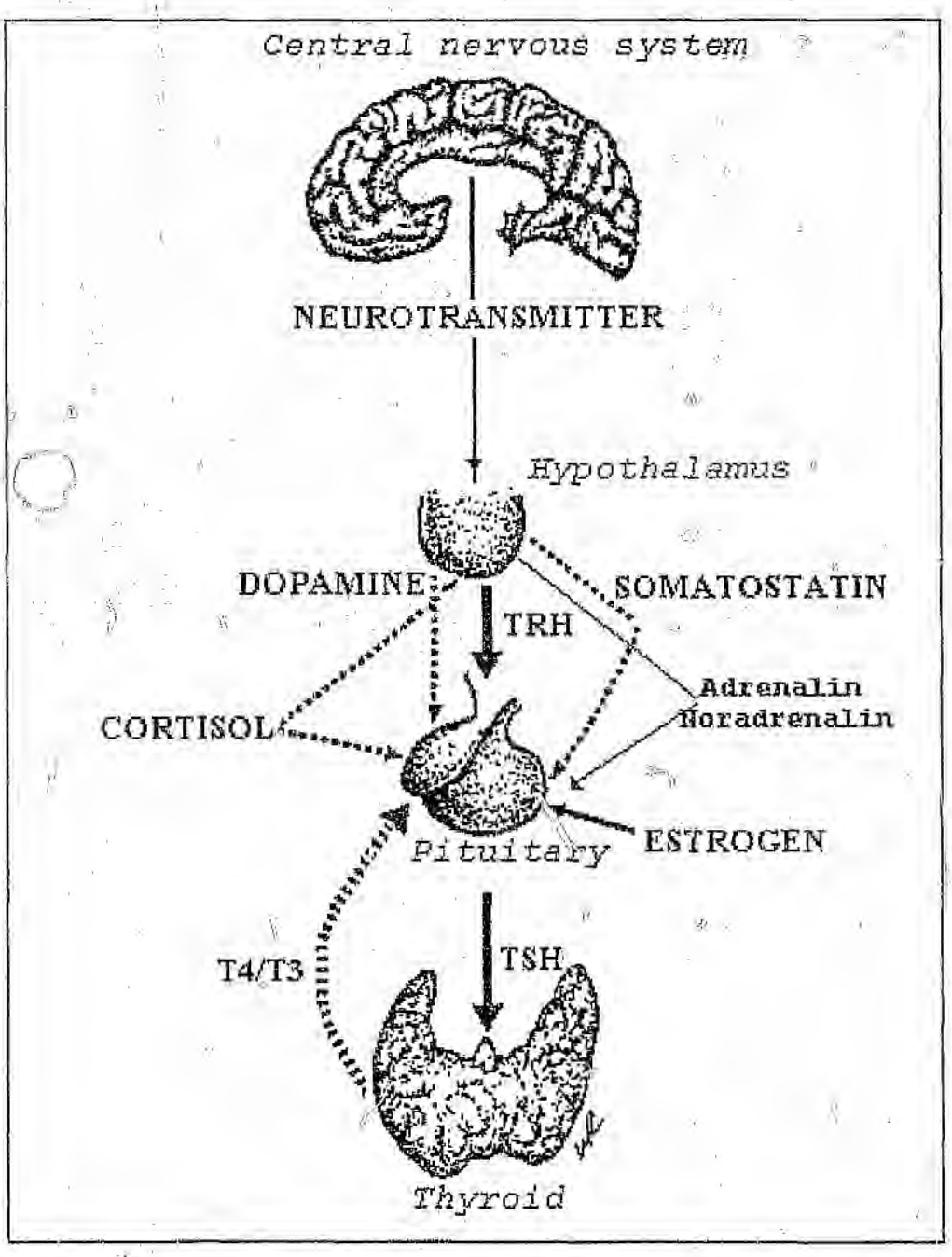


Fig 4. Schema of the hypothalamic-pituitary-thyroid axis and its hormonal control. Solid lines = + influence; interupted lines = negative inluence. Width of line represents relative importance of effect.

1.2.1 Thyroid Stimulating Hormone.

TSH is synthesised in the anterior pituitary and consists of a alpha and beta subunit. The alpha subunit is common to all glycohormones secreted from the pituitary, namely luteinizing hormone (LH), follicle-srimulating hormone (FSH) and human chorionic gonadotrophin (HCG). The beta subunit confers specific binding to the thyroid. TSH secretion is regulated by two major factors, (i) negative feedback from circulating thyroid hormones at the level of the thyrotroph cell, and (ii) stimulation by thyrotropin releasing hormone (TRH) from the hypothalamus (6).
TSH release follows a circardian rhythm, peaking at midnight (7) (Figure 10). Although in the peripheral tissues T4 is a prohormone for T3, at the pituitary level it has an important role in the regulation of TSH (8). Intra pituitary T3 is principally derived from circulating T4, thus TSH will rise in response to decreased levels of T4 despite normal or elevated serum T3 levels (9).

1.2.2 Thyrotropin Releasing Hormone.

TRH is a tripeptide produced in the paraventricular nucleus of the hypothalamus, and reaches the pituitary via the hypophyseal portal system. TRH binds to high affinity receptors on thyrotropes, and stimulates the release of TSH mediated via secondary messengers, ie cAMP and the calcium-calmodulin system (6,10). Tonic secretion of TRH is necessary to maintain thyroid hormone production (11).

1.2.3 Feedback Regulation of Thyroid Hormones.

The negative feedback of thyroid hormones occurs at the pituitary level. Both T3 and T4 bind to nuclear receptors in the thyrotroph, as they would in the target tissues (12). Due to the greater affinity of T3 (40 fold) for the nuclear receptor, its biological potency is much greater than that of T4 (20 fold) (13). About half of the intrapituitary T3 is derived from type II deiodination of T4 (14), and half is derived from circulating T3 (15). Basal TSH and TRH stimulated TSH release

are inhibited by binding of T3 to thyrotroph receptors (16). Circulating T4 is a more important regulator of TSH than T3 (9), and exerts its inhibitory effect via intrapituitary deiodination to T3. TRH probably determines the set point around which the thyrotropic T3 content regulates its control over TSH secretion (17).

1.2.4 *Neurotransmitter Regulation.*

Stimulatory and inhibitory secretory pathways for the control of TSH exist. Dopamine and somatostatin inhibit the release of TSH. Pharmacological doses of corticosteroids decrease TSH release. Adrenalin, noradrenaline, serotonin and oestrogen stimulate TSH release (Fig 4)(16). Encephalins and opiod peptides have a stimulatory effect, possibly acting via dopaminergic pathways.

1.3 *Thyroid Hormone Circulation and Transport.*

Less than 1% of the total circulating thyroid hormones is free in the plasma. T4 and T3 are 99.97% and 99.7% bound to thyroid hormone binding proteins (TBP) respectively. The TBP's include thyroxine binding globulin (TBG), thyroxine binding prealbumin (TBPA), and albumin (18). The binding of T3 and T4 to TBP's imparts a macromolecular status to the thyronines, which results in less renal loss and modulation of their effects on tissue metabolism. The TBP's act as a reservoir from which extra T3 and T4 can be mobilised (1).

Binding Protein.

TBG is a glycoprotein that binds 75% of total circulating T4. TBPA and albumin bind 15% and 10% respectively of circulating T4 (1). Even though albumin is a low affinity carrier, it has a large capacity to carry thyroid hormones due to its higher concentration (19).

TBG levels may be increased due to oestrogens, pregnancy, hepatitis, porphyria or heredity, and decreased due to androgens, cirrhosis, neohrosis or heredity (19).

An increase in TBG concentration, either genetic or aquired, results in an increase in unoccupied binding sites and a shift in the equilibrium between total and bound T4. The net effect is a diminution of the serum free T4 concentration. Activation of the hypothalamic pituitary axis occurs, resulting in a compensatory increase in thyroidal secretion of T4. The compensatory effects last untill a new steady state is reached i.e., a normal free T4 concentration. Thus the total extrathyroidal T4 pool is augmented owing to an increase in the intravacular T4 pool. The converse sequence of events occurs with a decrease in TBG (18).

Albumin, TBPA and TBG concentrations decrease with many illnesses. However this is insufficient to account for the marked reduction in serum TT4 levels that can occur. The prescence of an inhibitor is postulated to account for the deminished binding of thyroxine to carrier proteins (20).

Hereditary conditions associated with increased TBPA and increased binding to serum albumin also occur (1).

Free Thyroxine Hypothesis.

The original hypothesis of Robbins and Rall (21) stated that transport and uptake of T3 and T4 by the tissues was attributable only to the free fraction. This hypothesis has been questioned by Ekins (22) and Partridge (23). Ekins (22) has proposed a kinetic model in which bound T3 and T4 are important in delivery, particularly to tissues with high plasma clearance rates. The carriage of T4 by albumin into certain tissues may be of importance eg hepatic sinusolds.

1.4 Peripheral Metabolism of Thyroid Hormones

Thyroxine is metabolised by the sequential enzymatic removal of iodine molecules, predominantly in the liver and kidney. The delodination is accomplished by replacing iodine at one of four positions with a hydrogen atom. Iodine may be removed from the inner (tyrosyl) or outer (phenolic) ring (1).

Deiodination of T4 from the outer ring (5' or 5) yields T3. This pathway represents the activation of T4 to the metabolically more active T3 (24). Approximately 80% of circulating T3 is produced in this manner. Inner ring deiodination yields inactive reverse T3 (rT3) (fig 5)(25). Similar quantities of rT3 and T3 are produced per day by the deiodonation of T4 (18). Approximately 95-98% of rT3 is derived from T4 (76). In normal subjects the serum concentration of rT3 range from 30-50ng/dl (76). rT3 is metabolically inert (1). The peripheral turnover of rT3 is very rapid in comparison to T3. In normal subjects the metabolic clearance rate (MCR) ranges from 77-112 Litres/day/70 kg and the production/ disposal rates range from 34-52μg/day/70 kg (1). T3 and rT3 are deiodinated to diiodothyronines and eventually to thyronine. Released iodide is cleared principally by the kidney (80%) and by the thyroid (20%) (1).

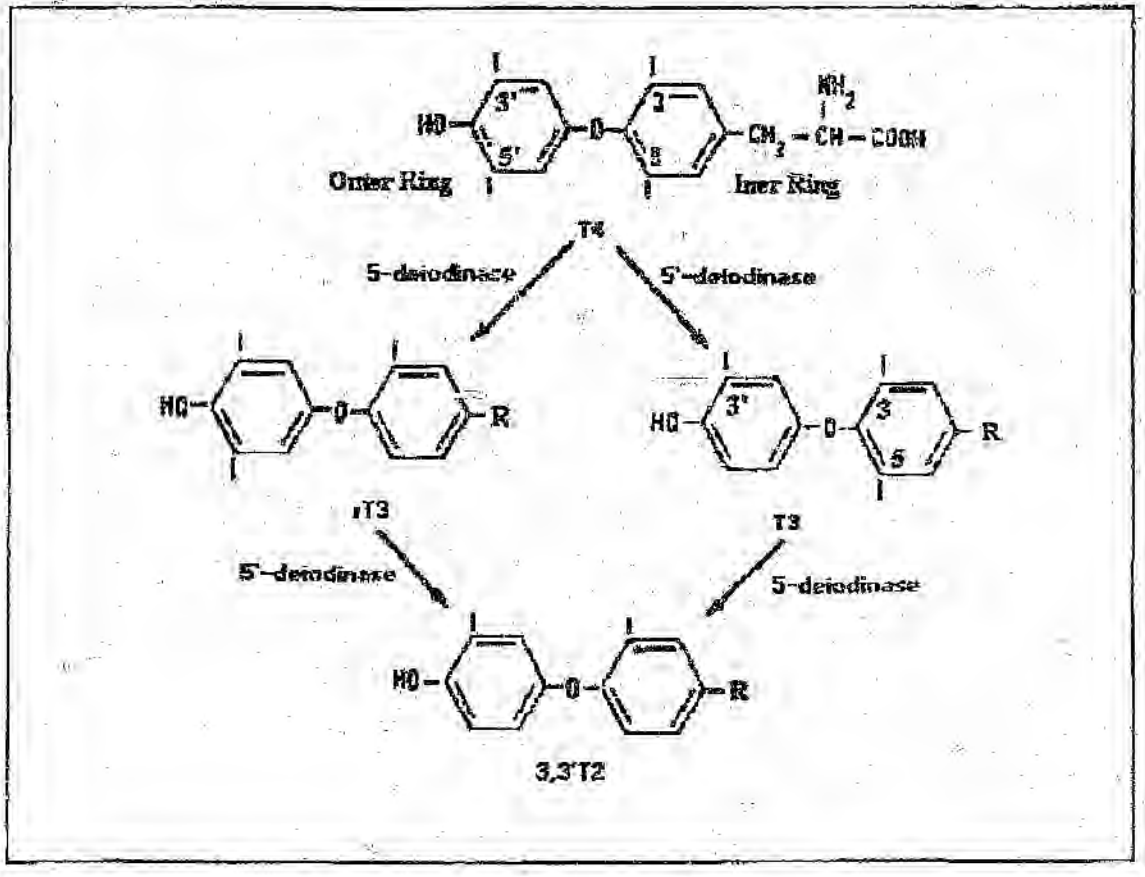


Fig 5. Thyroid hormone metabolism.

Three forms of iodothyronine deiodinase are recognised (26).

Type I catalyses both the inner and outer ring, but preferentially deiodinates the outer ring. It is present in liver, kidney and muscle, and acts preferentially on rT3 over T4.

Type II deiodinates the outer ring of T4 in preference to rT3, and is abundant in pituitary, brain, placenta and brown adipose tissue. Type III acts on the inner ring of T3 in preference to T4. It is diversely distributed in crude microsome fractions.

Perturbations of deiodination may occur under certain physiological and pathological conditions, in particular during fasting and stress.

Other pathways of thyroid hormone disposal exist, ie glucuronide conjugation and deamination of T3 and T4 to form tetra- and tri- iodothyroacetic acid (tetrac and triac) respectively (1).

The sulfated conjugate of T3 may serve as a metabolite of T3 for its rapid deiodinative disposal (27).

1.5 Thyroid Hormone Entry and Action.

Effects of thyroid hormone are evident in most organ systems. Nuclear receptor binding is thought to account for the diverse effects at a cellular level (4).

Thyroid hormone action can be viewed as a sequence of events: entry into the cytoplasm, movement into the nucleus and receptor binding and cellular responses (Fig 6) (1).

1.5.1 Membrane Binding.

Some passive diffusion of T3 and T4 may occur, in addition to a specific active transport system of limited capacity (28). A endocytotic process has also been proposed for T3.

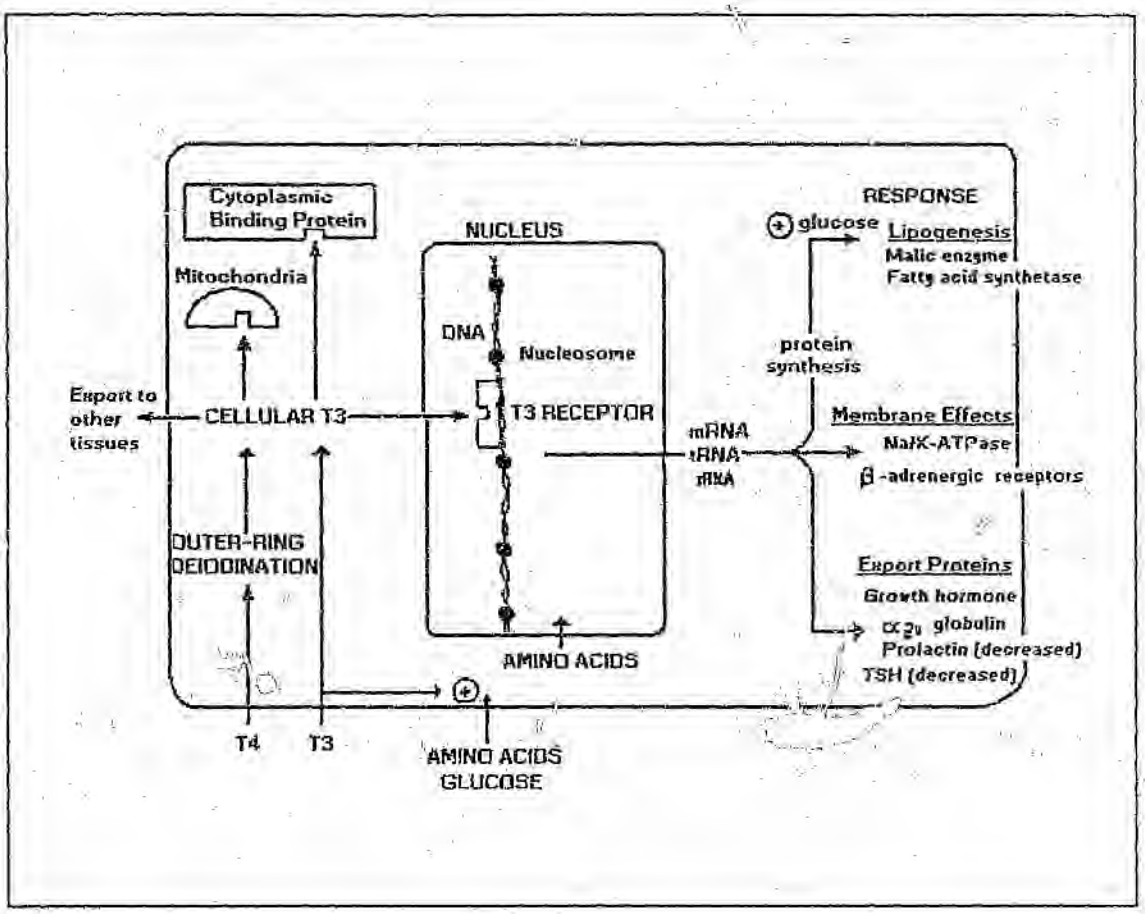


Fig 6. Cellular actions of thyroid hormones. Cellular T3 is derived from plasma T3 or T4. It may be exported to other tissues, bind to other intracellular proteins and organelles, or enter the nucleus. Nuclear effects are initiated with the binding to nuclear receptor on nuclear chromatin. Changes in RNA synthesis leads to changes in protein synthesis and a wide variety of cellular responses.

1.5.2 Cytosolic Binding.

Cytosolic thyroid hormone binding proteins probably function as an intracellular transport mechanism, as well as a hormone reservoir. Cytosolic TBP's bind T3 with a low affinity and high capacity (29). This steriospecific energy-dependent system increases the concentration of free T3 in the nuclei 50 to 200-fold over that present in the cytoplasm (18).

1.5.3 Mitochondrial and Nuclear Binding.

Both T3 and T4 bind to and initiate metabolic events within the mitochondria, but the relevance of this binding has been questioned because of low affinity and specificity.

With respect to nuclear mediated pathways, T4 is a prohormone for T3, which accounts for 90% of thyroid hormone in the nucleus.

The nuclear T3 receptor is an acidic nonhistone protein with high affinity and limited capacity, and a molecular weight of 50,5 kDalton (30). Cellular responses are determined by receptor occupancy. Nuclear T3 receptors are abundant in thyroid hormone responsive tissues, eg liver and kidney (1). The binding of T3 to the nuclear receptor induces changes in RNA polymerase and in the content of mRNA and tRNA.

1.5.4 Cellular Responses.

The metabolic effects of thyroid hormones can be divided into

(i) Catabolic: Thyroid hormone excess accelerates oxidative metabolism in most cells (2).

(ii) Anabolism: Lipogenesis is stimulated. Hepatic gluconeogenesis is increased. The anabolic function is required for normal growth and development of mammalian foetuses and neonates (31).

(iii) Permissive function: Thyroid hormones act in concert with or are required for the action of other hormones, eg. insulin and cortisol.

2.) THE "EUTHYROID SICK SYNDROME".

2.1) Introduction.

The effects of non-thyroidal illness on thyroid function was alluded to as far back as 1954 when Engstom and Markard (32) demonstrated that the protein bound iodine may be significantly reduced in severely ill patients. Oppenheimer et al (33) provided the first detailed analysis of alterations in thyroid function in patients with nonthyroidal illness. Subsequent to this our understanding of the "Euthyroid Sick Syndrome" has been facilitated by advancements in laboratory technology, specifically radioimmunoassay methodology, measurement of thyroid hormones and thyrotropin (TSH) and the availability of thyrotropin releasing hormone (TRH), for use in clinical investigation.

One of the most consistent features of the euthyroid sick syndrome is a reduced serum triiodothyronine (T3) level, which has been documented by a number of investigators, (34,35) occurring in 70 % of hospitalised patients (34)

Other characteristic features of the euthyroid sick syndrome include:

i) Increased rT3 levels in the presence of decreased T3 (36, 37).

ii) Normal (34) or low thyroxine (T4) level (38) which, in addition to a low T3, is referred to as the "low T4 syndrome".

iii) Increased, decreased or normal free thyroxine levels depending on the method of analysis (39,40,41).

iv) TSH is with in normal range except in a few cases (42). Serum TSH response to TRH is usually normal, though some patients show either an increased response or a subnormal and delayed response (38,43).

Because low serum levels of frequently measured thyroid hormones can be encountered in both hypothyroidism and the euthyroid sick syndrome, a lack of familiarity with the effects of non thyroidal illness on thyroid function tests may cause confusion in the interpretation of thyroid function in hospitalised sick patients.

2.2) Pathophysiology.

Patients with non thyroidal illness, resulting in the euthyroid sick syndrome may be divided into four groups (44) i) those with low T3 levels alone , ii) those with low T3 and T4 levels, iii) those with a high T4 level, and iv) those with a mixed form. A low serum T3 or low serum T3 and T4 levels are the thyroid function abnormalities most commonly seen in critically ill patients (fig. 7) (25).

The plausible mechanisms for the euthyroid sick syndrome and their effects in patients suffering from Nonthyroidal illness (NTI) are illustrated in Fig. 8.

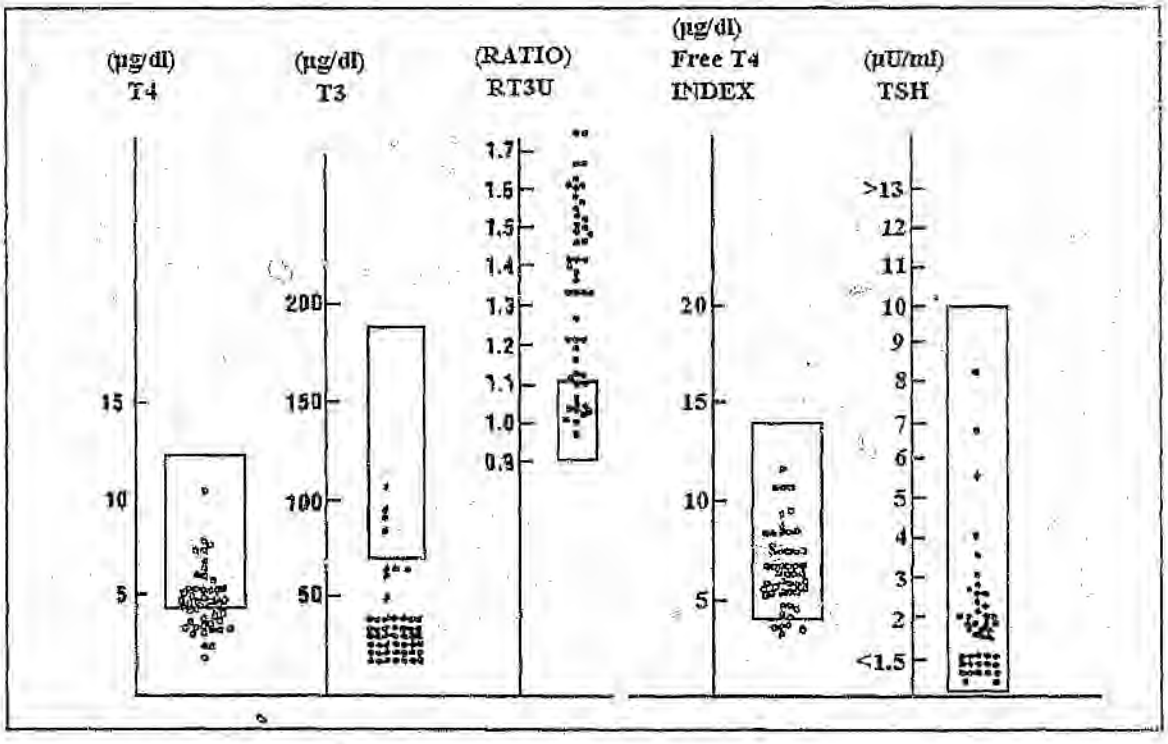


Fig. 7. Thyroid function tests in critically ill patients (25).

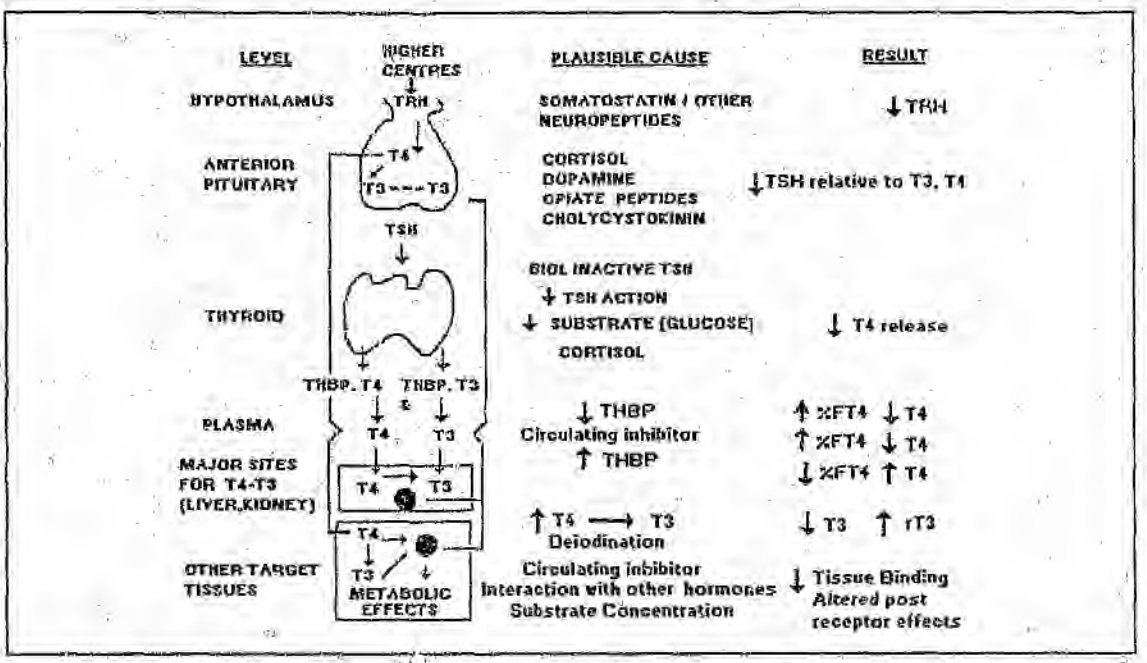


Fig 8. Pathophysiology of the euthyroid sick syndrome (44).

2.3 The low T3 syndrome.

The low T3 syndrome is characterised by a sub normal serum total T3 (34) and a normal serum T4. This abnormality is not specific for any particular disease (34,45). This syndrome may occur with various systemic illnesses such as liver disease, chronic renal failure, various infectious illnesses, neoplastic disorders, heart failure, burns, and stroke (34,37,46). A low serum T3 is seen in the vast majority of intensive care patients (44,47). It is also seen in patients following caloric deprivation (47,48), and after the administration of many drugs. In NTI the decrease in serum T3 is related to the severity of disease (46,49), and is due to a decrease in peripheral production of T3 from T4 (50). Thyroidal secretion of iodothyronines remains normal in the majority of patients with NTI (58). The T3 response to a TRH stimulation test is normal in patients with NTI (77). Concomitant with the decrease in T3 is an increase in rT3. Both these ch. nges are due to decreased activity of 5'monodeiodonase enzyme (fig.5) (35,41,51), deiodinase concentration (52) or both factors in combination (51). The decrease in

activity of the 5'monodeiodonase is thought to be due to a decrease in cellular glutathione, which is a co-factor for this deiodinase. secondary to decreased carbohydrate substrate (53,54), or increased glucocorticoid secretion, which partially blocks the conversion of T4 to T3 (55). The metabolic clearance rate of T4 and T3 is increased (36,56). Decreased rT3 disposal in the presence of unchanged production leads to the accumulation of rT3 in the circulation (35,39,41). The serum TSH level and the serum TSH response to TRH are usually normal, suggesting a euthyroid picture (43). Since serum T3 is significantly decreased in a large proportion of patients with non-thyroidal disease, measurements of T3 are of limited value in the diagnosis of thyroid dysfunction in patients with significant non-thyroidal disorders.

2.4 The low T4 syndrome.

The low T3, low T4 syndrome is seen in severely ill, often moribund, patients with a variety of systemic illnesses (37,53). Decreased serum concentration of total thyroxine in NTI are the net result of changes in hormone production (41), binding (41) and clearance(57). However the fluctuations in iodothyronine concentrations during NTI are mainly independent of thyroid secretion (58). The serum TSH and TRH response to TRH is usually normal. However there appears to be a functional disturbance of the hypothalamic-pituitary-thyroid negative feedback axis, with a degree of pituitary insensitivity to circulating T4 (38,51,57), or T3 levels (9). The low total T4 results from decreased serum binding (due to inhibitors), or a reduced fractional rate of transfer into tissues, which would impair the rate of clearance (56,57), and decreased T4 secretion from the thyroid gland (20,36,59).

2.4.1. Hormone Production and Kinetics.

In the normal individual, serum T4 concentration is maintained relatively constant as a result of the equilibrium between thyroidal T4 production and peripheral hormone degradation. Kaptein et al (56), using tracer kinetic studies, demonstrated that both the metabolic clearance

rate and fractional catabolic rate was accelerated in critically ill patients, but the derived T4 production rate was normal or only slightly decreased. They also demonstrated decreased binding of T4, T3 and rT3 to vascular and extravascular sites. As the rate of exit from the intravascular space was decreased, this would suggest a proportionately greater impairment of extravascular T4 binding.

2.4.2. Inhibition of T4 binding to carrier proteins.

Although Thyroxine Binding PreAlbumin (TBPA) and Thyroxine Binding Globulin (TBG) concentrations are decreased in many non thyroidal illnesses, this is not sufficient to account for the decrease in T4 levels (39,60). The free T4 level in NTI is normal or high (33,36,37,40,56). However the serum Free Thyroxine Index (FTI) may be deceptively low. These discordant results between the serum free T4 level and the FTI may result from the existence of an inhibitor of T4 binding to carrier proteins (20,59,60,61) which function normally in the free T4 assay (equilibrium dialysis) but not in the RT3U measurement (used to calculate the FTI). It is postulated that an inhibitor could occupy and reduce the number of functional T4 binding sites on carrier proteins, lowering the total T4 levels and increasing levels of free T4.

Tissue uptake of T4 is impaired due to the presence of an inhibitor in the serum (62). In 20-84% of the sera of patients with NTI the presence of an inhibitor has been documented (20,59). There is a small sub group of patients often critically ill, in whom Free T4 (FT4) by dialysis is low (36,56). Additional mechanisms other than a binding inhibitor must be invoked to explain these low FT4 levels, and various aspects of hypothalamic-pituitary control mechanisms have been implicated. Chopra et al (20,63) suggest that the inhibitor in NTI is non-dialysable, heat labile at 90°C and it can be precipitated by ammonium sulphate ([1.6 M]), and is abundant in the euglobulin fraction of serum. Chopra et al (41,61) also suggest that inhibitors of thyroid hormone binding are present in all cells and leak into the circulation from compromised tissue in serious illness. Nonesterified fatty acids (NEFA) are the most likely candidates as the inhibitor

for the following reasons,

* The concentration of NEFA may be increased several fold in NTI (64,65,66,67).
* In vitro NEFA bind to serum proteins, displacing thyroid hormones in a dose dependant manner (68,69,70)
* High levels of NEFA have been shown in vivo to decrease levels of TT4 and TT3 and to increase the dialysable (free) fractions (71).
* The following free fatty acids possess substantial inhibitory properties; arachidonic (most potent), oleic (contributes quantitatively more to thyroid hormone inhibition than the other circulating NEFA), lauric, linoleic and linolenic acids (20,61).

The inhibitor is more abundant in the particulate fraction (membranes) of tissue homogenates (61). It has therefore been postulated that in severe illness, there is activation of phospholipase A2, and as a result free fatty acids are released into the circulation, where they may inhibit the binding of T4 to plasma proteins, thus causing or contributing to the low T4 syndrome (72).

2.4.3 Bioavailability

Despite low circulating T4 and T3 levels, patients with NTI appear to be clinically euthyroid. The achilles tendon relaxation half time, basal metabolic rate, systolic time intervals and pulse wave arrival time remain normal in NTI (73,74). Controversy exists regarding the bioavailability of free thyroxine, as it is well established that in NTI thyroid hormone binding is altered and free thyroxine assays yield method dependant results. When considering the metabolic status in NTI it is important to bear the following points in mind, 1.) T3 and not T4 is the principal active form of thyroid hormone. 2.) extrathyroidal T4 conversion to T3 is clearly a regulated reaction. It may be altered as a result of changes in T4 availability, due to altered production of T4 or altered T4 uptake in deiodinating organs, changes in T4-5'deiodinase activity or amount, or changes in cofactor availability. 3.) T4-5'deiodinase activity varies from tissue to tissue and its

regulation also varies among different tissues. Tissue availability may be decreased as a result of a decrease in the albumin bound fraction (75) and the total thyroxine concentration (41). The normal or elevated free (dialysable) fraction of iodothyronines would suggest a normal delivery of hormones to the tissues. **In support of this concept is the observation that in NTI the extrathyroidal tissue production of rT3 from T4 is normal or minimally reduced (76,77), indicating adequate tissue availability of free T4 to sites of 5-deiodination.** By contrast the serum levels of total and free T3, the most metabolically active thyroid hormone, is frequently reduced, and that the free fraction of T3 does not reflect intracellular T3 levels (59). Grussendorf et al (58), claimed that intracellular iodothyronine concentration in livers of severely ill animals is not greatly altered in spite of marked decreased total serum levels, suggesting adequate T4 uptake from plasma or decreased degradation of T3. Oppenheimer et al (59) reported evidence that the factor inhibiting the binding of thyroxine to the circulating binding proteins reduces cellular accumulation of iodothyronines by tissues, and that the exchangeable cellular pool of hormone in NTI may not be proportional to the free T4 concentration as determined by equilibrium dialysis. This is in agreement with Pardridge et al (78) who found that in NTI thyroid hormone delivery to the liver was decreased, due to a reduction in the albumin bound fraction, which is also available for tissue uptake. Impaired binding of T4 to high affinity sites on hepatocytes has been demonstrated in NTI (78,79).

The paradox that exists in NTI i.e., a clinical euthyroid state in the presence of a reduced active form of thyroid hormone (free T3 and total T3) can possibly be explained by the following reasons, 1) normal intracellular T3 concentrations exist despite the depression in circulating serum T3 levels; such compartmentalization of T3 has been shown to occur in rat brain, pituitary, and brown adipose tissue secondary to local T4 to T3 conversion with in these tissues (8,80); 2) that quantitative and qualitative alterations in T3 nuclear receptors may occur such that lower concentrations of T3 may have an amplified effect (81); and 3) that there is a modification of thyroid hormone action on regulating peripheral tissue metabolism (82,83,84). whether any or all of these explanations may account for the apparent lack of hypothyroid symptoms and signs as well as the failure of TSH to be elevated is unresolved.

The action of thyroid hormones depends on the concentration of circulating T3, cellular uptake of T4 and T3, the number and affinity of T3-receptors and post receptor effects (85,86). The post receptor effects are complex and are mediated by variations in gene expression via mRNA in synergy with other hormones (87,88,89). By way of example Tibldi et al (90) studied rats with transplantable Walker 256 carcinoma, who had serum thyroid hormone levels similar to those of patients with NTI. In this study a decrease in nuclear T3 receptor numbers was also demonstrated (91). The responses of two thyroid hormone dependant hepatic enzymes were also studied ie; the mitochondrial enzyme, alpha-glycerophosphate dehydrogenase (alpha-GPD) and cytosol malic enzyme (92,93). Alpha-GPD activity is considered mainly under the control of thyroid hormone, where as malic enzyme is regulated by thyroid hormone and by insulin, glucagon, and nutritional factors as well. Alpha-GPD regulation was much more sensitive to T3 in tumour bearing rats. In contrast the appearance rate of malic enzyme was decreased in tumour bearing rats at all levels of occupancy of the T3 receptor. These findings are similar to those reported by Oppenheimer et al (82) in fasted rats, and suggest that post receptor factors such as nutritional status modulate specific cellular responses to thyroid hormone. Specific responses may become either more sensitive or less sensitive to prevailing levels of thyroid hormones. Thus in patients with NTI, enhancement of these biologic responses associated with the clinical manifestations of the euthyroid state may account for the normal clinical findings. Since the response of any specific biological parameter may be either enhanced or depressed by cellular factors that affect postreceptor mechanisms, it is probable that no single biochemical measurement will provide guidance to the thyroidal state of the entire individual during nonthyroidal disease (89).

The decreased extrathyroidal production of T3 in patients with severe NTI is thought to be an important adaption to illness in man (51). In NTI the decrease in serum T3 is associated with reduced muscle breakdown (94,95). Deminished T3 production may also result in reduced rates of oxygen consumption, substrate utilization, and various other catabolic processes (51).

2.4.4. Relationship of thyroid hormones to severity of illness and prognosis.

From longitudinal studies conducted in patients entering into and recovering from severe NTI, it is apparent that the alteration in serum thyroid hormone levels reflects a continuum (Fig.9)(18).

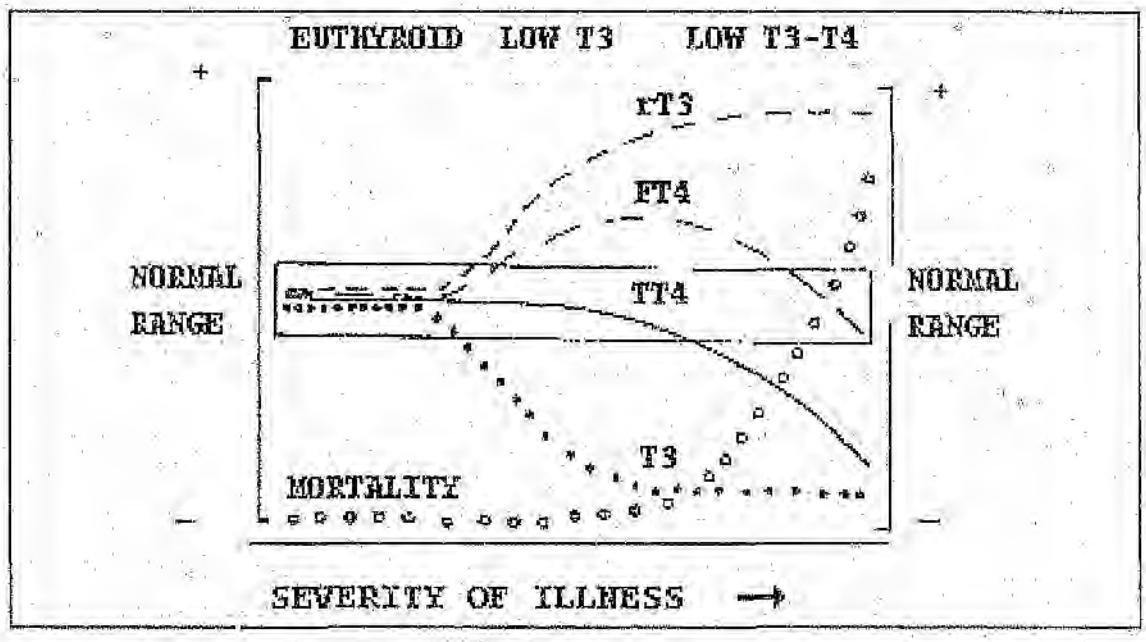


fig. 9: Schematic representation of the relative alterations in serum TT4, TT3, total rT3, and FT4 values in relationship to the severity of illness and mortality (96).

Patients with moderate severity of illness may have normal or decreased TT4 and free T4 index values with normal or increased free T4 by equilibrium dialysis (FT4D). As the severity of illness increases the patient becomes critically ill, the TT4 and free T4 index decrease further reaching very low values (low T4 syndrome). Recovery from illness or caloric deprivation (refeeding) is associated with normalisation of T3 (51,96). The magnitude of changes in thyroid function correlating with duration and severity of illness has been documented by a number of researchers (97,98,99,100,101).

The low T3 low T4 syndrome is found in 30-50% of patients admitted to a medical intensive care unit (46,102), and has been shown to be associated with a high mortality

(46,102,103,104,105,106). Kaptein et al (46), demonstrated that decreased TT4 had the highest correlation with mortality and correctly predicted outcome in 70% of patients. In patients with a nadir T4 value less than 3.0 μg/dl (38.6nmol/L), had a 68-84% mortality (46,105). Boles et al (103) have demonstrated a significant relationship between serum total T4, the Apache index (107), and death rate thus confirming the association between increasing quantified severity of illness, decreasing serum T4 and fatal outcome.

2.4.5. Therapeutic Implications:

Since there is no evidence to suggest the presence of reduced free T4 availability during the low TT4 state of NTI, thyroxine replacement therapy is not indicated. Neither L-thyroxine nor L-triiodothyronine administration has been shown to be of any benefit (108,109), and may be detrimental. Thyroxine (T4) Supplementation in rats infected with Streptococcus pneumoniae shortened their survival time (110). However Dulchavsky et al (111) found that treatment with T3 preserved respiratory function in septic rats as evidenced by respiratory drive and compliance.

Administration of T3 to experimentally starved persons with low T3 levels accelerates protein and fat catabolism (109,95). Thus patients with reduced free T3 and free T4 indexes secondary to NTI should not receive thyroid hormone therapy Instead the main goal of therapy should be treating the primary disease state and providing adequate nutrition to minimise catabolism. The spontaneous normalisation of serum TT4 and TT3 levels may provide an indication of the effectiveness of these therapeutic endeavours (1).

2.5. Euthyroid Hyperthyroxinaemia: the high T4 syndrome.

Patients with a variety of NTI may have a elevated serum TT4 and free T4 index values (112). Free T4 index has been reported to be elevated transiently in patients with mild nonthyroidal illness, including the elderly sick patient, those with liver disease, or psychiatric disorders (77).

The commonest cause of the increase in TT4 in this group of patients is an increase in TBG concentration (113). The total T3 may be increased or normal, but the free T3 is reduced due to the decreased peripheral deiodination of T4 to T3. The serum TSH level and the TSH response to TRH is normal (113). Liver disease, in particular infectious hepatitis, chronic active hepatitis, and primary biliary cirrhosis, may increase TBG levels (114,115).
These changes may also occur in acute psychiatric illness, or be drug induced, eg. oestrogens, narcotics, clofibrate, 5-flurouracil (25,113). These changes are generally transient and tend to normalise on recovery from the NTI (1).

2.6 The Hypothalamic-Pituitary axis in NTI.

Alterations in the hypothalamic-pituitary-thyroid negative feedback axis may account for some of the changes observed in circulating thyroid hormones (116). Although basal TSH levels are normal, and there are reports documenting a normal TSH response to TRH (41,95), evidence does exist that the regulation of TSH in NTI is disturbed. Franlyn et al (117) demonstrated a failure of TSH to rise despite decreased levels of iodothyronines in patients with myocardial infarction, indicating a failure of negative feedback effect. Wehmann et al (118) documented a reduced basal serum TSH level in the majority of patients who had undergone bone marrow transplantation and who had decreased serum levels of T4, T3 and FT4, thus suggesting that the decreased TSH secretion contributed to the decrease in serum T4 and T3 levels, in these patients. During the stress of illness many hormones are released, such as cortisol, dopamine, growth hormone, and opiate peptides, which inhibit the release of TSH from the pituitary (44,119). Caloric deprivation may decrease TSH release and the TSH response to TRH may be blunted (120,121).
Martulo et al (122) demonstrated that the TSH response to TRH in NTI is not normally augmented by reductions in T4 and T3 by the administration of iodides.
In tumour bearing rats it has been found that TSH regulation remained normal despite a decrease in pituitary nuclear T3, suggesting that the set point for TSH regulation is shifted

towards a lower T3 value, ie the pituitary response to T3 is augmented (83).

A subset of patients exists that may have elevated or depressed TSH levels. Mild to moderate elevations in basal TSH have been documented in NTI, particularly in the elderly, and tend to return to normal on recovery from the acute illness (34,37, 42,45). During the recovery phase of NTI there may be a transient elevation of TSH (116,123) and the TSH peak may rise above normal and precedes the return of low T4 levels to normal.

During critical illness TSH levels may be depressed and even become undetectable when using a high sensitivity assay (124), and the TSH response to TRH may be blunted (38).

3.0 Miscellaneous Factors Associated With Altered Thyroid Hormone Economy

3.1. AGE.

Advancing age is associated with an altered thyroid hormone economy. The metabolic clearance rate and T4 turnover are decreased (125), as is the serum T3 level (126), but the serum T4 level is normal (126), or slightly reduced (127), in the elderly. There is a decrease in iodine uptake and consequent decrease in T4 secretion from the thyroid in the elderly (76). Free T4 concentrations are usually normal (127), but serum TBG levels increase with age (128). Basal TSH levels are normal or increased, and the TSH response to TRH may be blunted (127,129).

3.2 Stress response to surgery and trauma.

Changes in serum thyroid hormones in surgical and traumatic stress states is analogous to that seen in NTI. The serum total T4 decreases, while free T4 decreases or remains unchanged following surgery (130). Serum total and free T3 fall rapidly after surgery, and is related to the severity of the surgical trauma (131,132). There is evidence to suggest the presence of a protein binding inhibitor in post operative patients (132,133). Reverse T3 is increased following surgery (131,133). Serum TSH is usually normal (131,132), and the TSH response to TRH may be increased (134), unchanged (132), or decreased (133), on the first post operative day. Brandt et al (135) refuted the previously held belief that the surgically stimulated release of cortisol is responsible for the observed postoperative alterations in T3, rT3, and TSH. Burn patients show a similar alteration of their thyroid hormones in that T3 is decreased, rT3 is elevated, and the dialysable fraction of T4 is increased, and TSH is normal or low (136).

3.3 Drugs

The effect of drugs on thyroid hormone economy has recently been reviewed (137). Many drugs affect thyroid function tests through alteration in the synthesis, transport and metabolism of thyroid hormones, in addition to influences on TSH synthesis and secretion. Commonly prescribed drugs, including those used in the treatment of critically ill patients, may result in abnormal thyroid function tests, without causing clinically detectable changes in the thyroid status of the patient (137). This often contibutes to difficulties in the diagnosis of thyroid dysfunction, in these patients. However it is important to remember that a few drugs, particularly lithium (138) and those containing iodine (139,140), are associated with the development of clinically significant thyroid disease.

Peripheral metabolism (deiodination) is affected by certain drugs (141,142). Glucocorticoids (55), propranolol (143), amiodarone (144), radiopaque dyes (145), and propylthiouracil (146) all inhibit the 5'-deiodination of T4. The concentration of TBG may be increased by oestrogens (147), heroin and methadone (148), clofibrate (149), or decreased by androgens and anabolic steroids (150), and glucocorticoids (151).
Interference with thyroid hormone binding to TBG, nd / or TBPA may result from phenytoin and its analogues (152), sulfonylureas (153), and salicylates (154). Serum TSH or its response to TRH may be increased by dopamine antagonists eg metoclopramide (155), lithium (138), and iodine and iodine containing compounds, eg radiographic contrast material (145), or decreased by dopamine (155), glucocorticoids (156), and morphine (157).

For a summary of the effects of commonly used drugs on thyroid function refer to Table 1.(137,25).

Table 1. Effects of drugs on thyroid function tests

Drug	T4	FT4	T3	rT3	FT3	TSH	TRH TEST
Dopamine	-	-	-	N	-	-	-
Glucoco-corticoids	-	N	--	++	?	-	-
Radiopaque dyes	N/+	N/+	--	++	-	N/+	N/+
Propranolol	N	N/+	-	+	-	N	N
Amiodarone	+	+	--	++	-	N/+	N/+
Phenytoin	-	N/-	N/-	N/-	-	N	N
Salicyiates	-	N/+	-	N/-	+	N/-	N
Heparin	?	+	?	N	+	-	?

Symbols: + = increased; - = decreased; N = normal;
? = unknown.

3.4 Starvation and fasting.

The changes that occur in serum thyroid hormone levels with fasting have served as a useful model in understanding the pathophysiology of the euthyroid sick syndrome. Longitudinal studies in fasted subjects have revealed that the first change to be observed is in free T4 (FT4). Within 14 to 18 hours of fasting there is a small but significant rise in FT4 levels, which is sustained through out the fast. Shortly following the rise in FT4, there is a fall in serum T3 (158), which continues to drop progressively over the next four to seven days to reach a new steady state level approximately half that of the baseline level. Serum TSH levels fall abruptly after 24 hours of fasting, and the TSH response to TRH, at this stage is blunted (159). The serum TSH levels then gradually increase, indicating an apparent increase in the sensitivity of the thyrotrope to the negative feed back signal of the reduced circulating level of T3 (160). Serum rT3 levels only begin to increase after the third day of fasting, but then subsequently decline to, and reach normal values after two to four weeks of continued fasting. The changes in serum T3 and rT3 with fasting demonstrates clearly that there is no inherent reciprocosity of changes in serum T3 and rT3 levels. The changes that occur in serum thyroid hormones with fasting are demonstrated graphically in figure 10 (158).

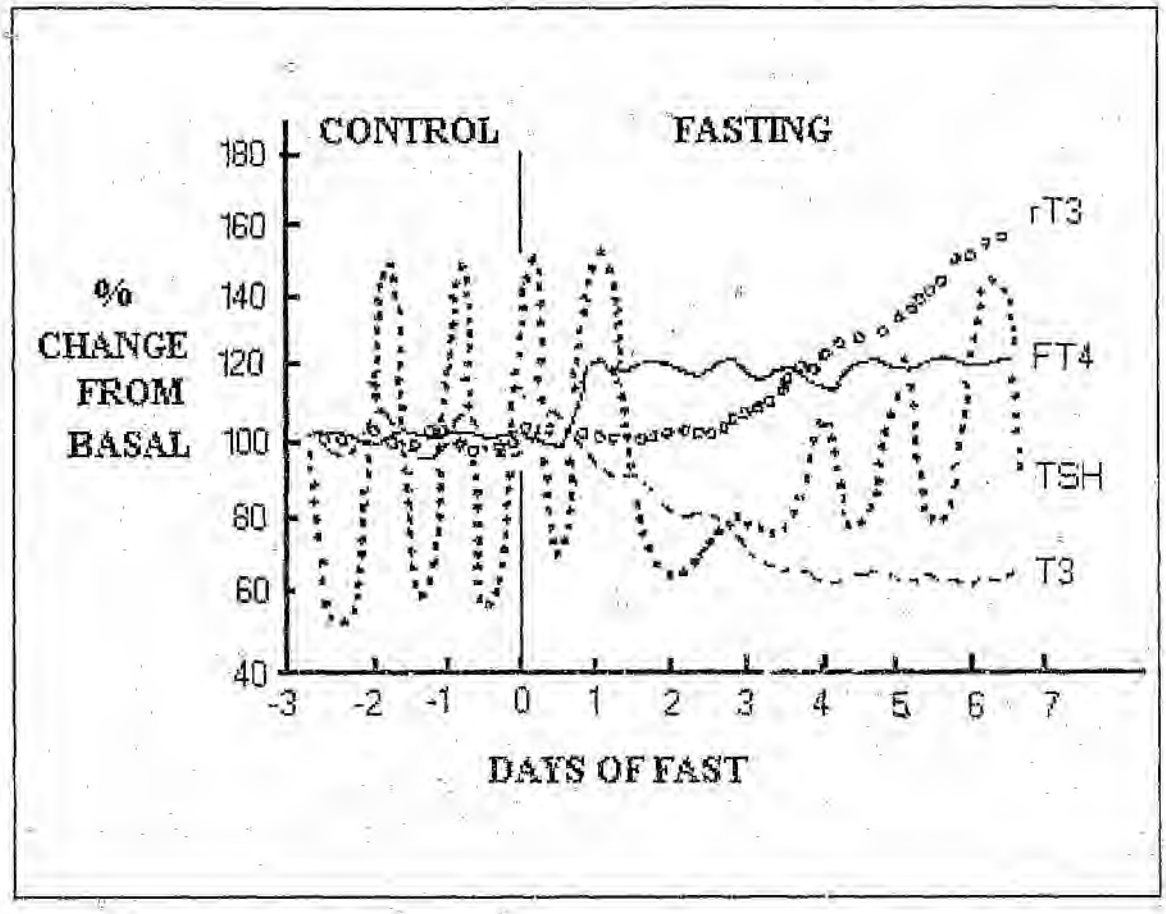


Fig. 10: Schematic representation of alteration in serum TSH, FT4, T3, and rT3 with fasting in man.

Carbohydrate restriction is the most important factor in the pathogenesis of the observed changes in thyroid hormone economy with fasting (76). Refeeding with minimal glucose ingestion (50 g/day) can reverse the fasting induced alteration in serum T3 and rT3 levels (161), where as refeeding with fat (162), or protein (47) do not. The decline in serum T3 is of physiological importance in that it appears to facilitate conservation of the bodies protein stores, since when serum T3 values are normalised by exogenous T3 administration, there is a significant increase in nitrogen losses (94). In critically ill patients, a large component of the alterations in thyroid hormone levels may be due to the caloric deprivation associated with such severe illness (160,163).

3.5 Liver disease.

The liver is central to thyroid hormone economy, due to its role in the synthesis and metabolism of plasma binding proteins (TBG, TBPA, and albumin)(164), and the deiodination and conjugation of thyroid hormones (85). Thus the alterations in circulating thyroid hormone levels will be determined by the severity and nature of the hepatic disorder.

In cirrhosis, the thyroid abnormalities depend in part on the amount of functioning liver tissue. The TT4 may be normal or slightly decreased (165), FT4 and rT3 are increased, and TSH level are usually normal but may be elevated (76). The production rate of T3 may be reduced by half (166). The presence of hyperamonaemia has been shown to increase the TSH response to TRH, possibly due to the portosystemic shunting and hepatic encephalopathy (167).

Infectious hepatitis is associated with normal or elevated T3 and T4 levels as a result of an elevation in TBG, and decreased hepatic T4 uptake. Free T4 is normal, rT3 is elevated, basal TSH is normal or low, and the TRH stimulation test is normal in these patients (76). In chronic active hepatitis the serum TBG concentration is increased resulting in elevated levels of T3 and T4. The free T4 level is low, TSH is elevated, and the TSH response to TRH increased.

Patients with hepatocellular carcinoma may have elevated TBG levels both in the presence or absence of cirrhosis, with reduced binding of T4 to TBG (168).

In summary therefore liver diseases, except for acute viral hepatitis, have elevated free thyroxine levels in common with other non thyroidal illnesses. The TBG and TT4 may be slightly higher than that seen with other non thyroidal illnesses.

3.6 Renal Disease.

Chronic renal failure influences thyroidal economy at every conceivable level. Impaired iodide excretion occurs in renal failure, resulting in increased concentrations of circulating iodide and increased thyroidal uptake (169). The kidney is also an important site of T4 degradation.

In the nephrotic syndrome thyroid hormone is lost in the urine, resulting in low serum T4 and

T3 levels. Most of these patients are euthyroid as evidenced by normal serum free T4, RAIU, serum TSH, and TSH response to TRH (76). Rarely a patient may have a low T4 level associated with massive proteinuria, elevated serum TSH levels and a goitre.

In chronic renal failure the serum levels of T3 are low due to decreased peripheral conversion of T4 to T3; however rT3 levels are usually normal (76). During the development of uraemia the binding of T4 to TBG is reduced, and to TBPA is increased (170). As the patients renal status deteriorates the serum T4 levels decline. Serum free T4 levels are usually normal or decreased and tend to correlate with the severity of renal failure. The TBG may be decreased in patients with proteinuria resulting in a normal or increased RT_3U. Serum TSH is usually normal, but the TSH response to TRH is blunted or delayed (171).

Patients on chronic haemodialysis tend to show the same general values for serum T4, T3, FT4, and TSH, as patients with chronic renal failure (76). Changes observed in dialysis depend on whether observations were made acutely or following chronic dialysis. Kalk et al (172), noted acute improvement in serum T4, T3, and FTI but no change in TSH, whereas other workers have reported no improvement in T4 , PBI, T3 (173), or in basal TSH or TRH responses(173). Following renal transplantation there is a normalisation of essentially all abnormal thyroid function parameters (98,174).

3.7 INFECTION

Following the onset of almost any infection serum T4 and T3 decrease as a result of decreased TSH stimulation of the thyroid and thyroidal secretion, accelerated T4 disappearance and inhibition of hormone binding to transport proteins (175,176). Serum FT4 and rT3 are increased and TSH is normal (177).

Richmand et al (177), when assessing the relative roles of caloric deprivation and infection per se in the genesis of the alterations in thyroid function tests, concluded that caloric deprivation was contributing as much to the observed changes in thyroid status as was the infection. The basal metabolic rate (BMR) in sepsis is increased, in contrast to the decreased BMR that occurs

in other nonthyroidal illnesses (177).

Minor differences in results have been observed in certain types of infection. Maharajan et al (178) noted in their patients with meningitis and typhoid fever a tendency toward a slight increase rather than a decrease in serum total T4. Talwar et al (179) observed a decreased T3 and normal TSH, without any change in TT4 despite a significant decline in TBG capacity. The thyroidal abnormalities correlated with the severity of infection. A reciprocal relation existed between the height of the fever and the serum T3 level. With uncontrolled infection and increasing fever Talwar et al (179) demonstrated an increased percent FT4, absolute FT4, and percent FT3. The data strongly suggests that TSH release is suppressed with infection (180,181,182,183). It is not clear however whether the enhanced cortisol production and relative caloric deprivation may be responsible in toto or in part for the suppression of TRH or TSH release.

Changes in thyroid hormone economy in sepsis, as defined in this study (see chapter 5.0), have only recently appeared in the literature. Hadjikostova et al (184) induced septic shock in rats by cecal incision, and documented a significant decrease in T3 and T4 by the fifth hour of septic shock. By the tenth hour thyrotropin and prolactin were also significantly decreased. Dennhardt et al (185) investigated 15 patients who became septic postoperatively. In addition to a high rT3 and low T3, septic patients were characterised by a high DIT. DIT appears to be a relatively specific parameter for the presence and cource of severe bacterial inflammations (186).

Tumor necrosis factor-alpha (TNF-α) and interleukin-1 are important mediators of the sepsis cascade (see chapter 5.2.1). Present data indicate that TNF-α is one of the mediators responsible for alterations in thyroid function tests in patients with nonthyroidal illnesses (187,188,189), but not interleukin-1 (189).

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4.0 Tests of Thyroid Function in NTI.

Thyroid function tests are normally requested in order to determine the thyrometabolic status of the patient, ie hyperthyroidism, hypothyroidism or euthyroid. Numerous factors may affect both the function and available tests for the assessment of the hypothalamic-pituitary-thyroid axis. These include physiological, pathological, pharmacological factors, and assay methodologies all of which may result in a bewildering array of alterations in serum thyroid hormone concentrations. In order to be able to interpret thyroid function tests in NTI, it is essential to have an understanding of the methodology and deficiencies of each test.

4.1 Total Thyroxine (TT4)

Total thyroxine can be reliably assessed by a radioimmunoassay (RIA); the normal range in most laboratories is 4.8-12.8μg/dl (62-165nmol/L). The RIA method depends on the stripping of T4 off the TBP's and then on the competition between total thyroxine in the serum and [^{125}I]thyroxine for a limited number of binding sites on a T4 specific antibody, and measures both free and protein bound T4. As a result of this, an increase in TBG will result in an increase in serum TT4 levels. A decrease in TBG or other thyroid binding proteins decreases the TT4 levels. In NTI TT4 levels may be normal, low, or high. Total T4 levels in isolation may therefore be misleading for the assessment of the thyrometabolic status of the patient.
Other methods of determination include fluorescence, fluorescence polarisation, chemiluminescence, gas chromatography, HPLC and enzyme immunoassays (190).

4.2 Total Triiodothyronine.

Serum T3 is also determined using a RIA technique. The T3 assay also measures both free and protein bound fractions, and is influenced by protein binding abnormalities. A low T3 is the hall

mark of NTI.

4.3 Free Thyroxine Index.

The FTI is a calculated estimate of free thyroxine concentration. It is the product of TT4 concentration and the T3 resin uptake (RT3U). The RT3U is performed by incubating radiolabeled T3 with the patients serum. Some of the exogenous T3 binds to available protein binding sites. Following appropriate washing, a resin is added that is capable of binding only unbound radiolabeled T3. Radiolabeled T3 attached to the resin is inversely proportional to the T4 binding capacity of TBP's. The normal range is 33-48%. The RT3U is not related to serum T3 levels, since the affinity of TBG for T3 is low compared to that of T4. RT3U is elevated in hyperthyroidism and with decreased TBG levels. A low RT3U occurs with hypothyroidism and increased TBG levels.

The FTI is used as a means of compensating for changes in TT4 level that result from abnormalities in protein binding. In NTI the FTI is generally low in up to 23% of random hospital admissions (37,60). This is contrary to what one would expect, if one assumes that in NTI many of the binding sites on TBG are occupied by an inhibitor. One would then expect that the RT3U be markedly increased and the FTI be normal or elevated, however this is seldom seen. Several explanation for this phenomenon have been proposed.

(i) T3 binds proportionately more to albumin than TBG, which in NTI is reduced more than TBG.

(ii) RT3U is measured at an acid pH, which may inactivate the inhibitor of thyroid hormone binding to TBP's.

(iii) the inhibitor could inhibit the binding of radiolabeled T3 to the resin (37,61).

In conclusion therefore the FTI, as an estimate of free thyroxine levels, yields a high proportion of false positive results in NTI, when compared to free thyroxine measured by equilibrium dialysis.

TBG can also be assessed directly by using a RIA. The T4:TBG ratio will also correct for alterations in TBG levels (191). The ratio correlates well in patients with normal albumin and TBPA, but performs poorly when these proteins are abnormal or TBG is low (17). The T4:TBG ratio correlates with the FTI and FT4 for simple thyroid disease and euthyroidism with out NTI (190).

4.4 Free thyroid Hormone Measurements.

Measurement of FT4 will exclude problems of protein binding encountered with TT4 assays. However the measurement of FT4 is not without its problems as its measurement is influenced by physicochemical factors in vitro.

4.4.1 Equilibrium Techniques

Equilibrium techniques may be defined as those in which the assay system attains thermodynamic equilibrium across a membrane or partition phase, and the final measurement depends on the distribution of hormone between the free and bound state or the absolute amount of hormone in the free moiety.

Equilibrium dialysis stands as the "Gold Standard" against which other methods of establishing FT4 are validated. However the test is cumbersome (75) and vulnerable to radiochemical impurities (192).

Equilibrium techniques may be divided into direct and indirect techniques.

Indirect: Requires the measurement of TT4 by RIA. The free fraction is derived by equilibrium dialysis and the results expressed as indices ie. percent free T4 (that which has dialysed across the membrane) * the TT4 = absolute FT4.

Direct: In this method the free hormone fraction in the serum dialysate is measured directly using a highly sensitive RIA. Direct dialysis methods usually give lower values than indirect dialysis methods and provide the best estimate of free thyroid hormone concentrations, since they are not affected by impurities in the tracer in the measurement (193).

4.4.2 Nonequilibrium Techniques: Radioimmunoassay.

Analog Free Thyroxine.

Analog assays are based on the principle that RIA of the free fraction in whole serum is possible if a structurally modified radiolabeled form of the hormone is used which does not bind to serum proteins, yet at the same time retain an affinity for the antiserum comparable to that of the unmodified ligand.

A number of commercial analogue assays are available, notably Amersham Corporation, Becton Dickinson, Clinical Assays, Corning, Diagnostic Products. They have proved to be convenient and readily applicable to large batch assays. They are reproducible and cost effective (194).

The advantage of the analog radioimmunoassays is that because the analog T4 supposedly has a very low affinity for the normal T4 binders in serum there is no disturbance of the equilibrium between T4 and the binders (195). However studies exist that substantiate the view that the first generation analogue assays are albumin dependent, and possibly that the high affinity antibody used in some kits significantly disturbs the free/bound hormone equilibrium (190). Second generation analogue assays now exist that are alleged to have reduced albumin binding interference (196).

Most studies demonstrate a reduced FT4 using the analogue method in patients with NTI, when compared to equilibrium dialysis techniques (39,40,197).

Two-Step Free Thyroxine Radioimmunoassay.

This assay was developed by Ekins et al (198) and produced commercially by the Clinical Assays division of Travenol Laboratories. This assay is based on an immuno-extraction technique using solid phase antibodies. This method is said to be less affected by protein binding effects than the analogue methods. This assay is reported to yield higher values than other FT4 assays (199) and to correlate better with equilibrium dialysis.

4.5 Free Triiodothyronine.

Due to the commonalities for T3 and T4 and the limited application of T3 assays for clinical diagnosis it is unnecessary to review T3 assays in depth.

Available methods for determining FT3 include equilibrium dialysis followed by sensitive RIA of the dialysate. Amersham International have commercialised the FT3 assay using an analog method. This assay is however albumin dependent (200).

4.6 Basal Serum TSH.

RIA methods: first became available in the 1960's but their clinical use was limited due to lack of sensitivity and specificity. Routine RIA have a sensitivity of 1-3 mU/L, with the lower limit of the normal range being undetectable levels , indistinguishable from A proportion of normal patients have suppressed TSH levels found in hyperthyroidism (201).

Labelled antibody immunoassay for TSH: provides an alternative approach to RIA and has provided major advances in sensitivity, specificity and speed of TSH assay. These advancements have also enabled the previously undetectable lower range of normal to now be identified.

The immunoradiometric assay (IRMA) uses a combination of two monoclonal antibodies, each of which is specific for a different epitope of the TSH molecule. One antibody is bound to a solid matrix and the other is radiolabeled. A radiolabeled "sandwich" is formed by the simultaneous binding of the antibodies to TSH. The serum concentration of TSH is directly proportional to the radioactivity in the "sandwich".

Several variations of this technique are possible. For example, immunoenzymometric assay, immunochemiluminometric assay and immunoflurimetric assay. The sensitivity of these assays vary from 0.2-0.004 mU/L (201).

Clinical indications. Evidence now exists that the basal TSH is a reliable indicator of thyrotroph activity across the entire spectrum of thyroid disease. TSH can therefore be used reliably as a screening test of thyroid function, including subclinical primary hyperthyroidism and hypothyroidism. TSH is also not subject to protein binding effects, and has fewer in vivo and vitro drug effects.

Ultra sensitive assays are able to diagnose hyperthyroidism in over 90% of cases, thus obviating the need for a TRH stimulation test to diagnose mild hyperthyroidism (1).

5.0 SEPSIS.

The exact frequency of sepsis is not known, but estimated to between 70 000 and 300 000 cases in the USA each year (202). Once the complications of sepsis occur, in particular septic shock and multiple organ failure, clinical deterioration is rapid, usually associated with a high mortality rate (202). Kreger et al (203) reviewed 612 patients with gram negative bacteraemia and found that the early institution of appropriate antibiotics reduced the incidence of septic shock by nearly 50% and reduced the mortality rate. This study highlights the need for the early recognition and treatment of sepsis and it's complications. This is of particular importance in the modern intensive care setting with the use of invasive techniques and immunosuppressive therapy, which predispose to sepsis.

5.1 Definitions.

Humpty Dumpty in Alice in Wonderland stated that " words mean what I say they mean". Confusion exists in medical literature regarding sepsis, due to differences in meaning when using the same terminology. A need has therefore arisen to obtain consensus on definitions, so that comparison of clinical and therapeutic trials may be adequately performed. Professor RC Bone has spearheaded the quest for linguistic precision (202,204,205), and has suggested the following definitions of sepsis.

Bacteraemia. The presence of viable bacteria in the blood. A positive blood culture is the diagnostic criterion.

Septicaemia. Has been used too generically to denote any blood borne infection, and its use is now considered obsolete.

Sepsis. The suspicion of infection plus the systemic response to it as evidenced by tachypnea (respiration >20 breaths/min; if mechanically ventilated, minute ventilation >10 L/min), tachycardia (heart rate >90 beats/min), and hyperthermia or hypothermia (core or rectal

temperature >38°C or <35.5°c).

Septic Syndrome. Sepsis with evidence of altered organ perfusion, as evidenced by (i) acute changes in mental state (ii) hypoxia (arterial oxygen tension < 75mmHg, without other pulmonary or cardiovascular disease as the cause) (iii) increased serum lactate concentration (iv) oliguria (documented urine output < 0.5 mL/Kg body weight for at least 1 hr).

The septic syndrome can be produced by both gram-positive and gram-negative bacteria, pathogenic viruses, fungi and rickettsia, and other noninfectious inflammatory states e.g., pancreatitis and trauma. It is important to note that blood cultures need not be positive, as demonstrated in the study of septic syndrome by Bone et al (202), where only 45% of blood cultures were positive.

Septic Shock. Sepsis syndrome with hypotension (systolic BP <90mmHg or decreased from baseline systolic BP >40 mmHg), that is responsive to intravenous fluids or inotropic therapy.

Refractory Septic Shock. Sepsis syndrome with hypotension that lasts for >1 hr, and is unresponsive to iv fluids (500 mL of normal saline over 30 mins) or inotropic therapy (e.g.,dopamine>10 uKg.min).

Bone et al (202,206) demonstrated that the rate of shock development for bacteraemic patients was significantly higher than for nonbacteraemic patients (47% vs 29.6%). Kreger et al (207) found that 44% of their bacteraemic patients developed shock, and this resulted in the mortality rate increasing from 7% to 47%. Whereas Bone et al found that the mortality rates in patients with septic syndrome compared to patients with septic shock were 13% and 34% respectively (202). The mortality rate of septic shock ranges from 10% to 90% in most reviews (204,207). The divergent rates of mortality can be attributed to variable definitions of sepsis and septic shock. Locally reported mortality rates of 40% in septic shock patients are reported by Smith et al (208), from the Hillbrow Hospital ICU.

Multiorgan Failure. Multiple organ failure may result from severe sepsis, and is associated with an extremely poor prognosis (209).

The above definitions were used in the research protocol, and will be adhered to in further discussion.

Although the definitions are an attempt to obtain clarity in existing terminology, consensus has not been reached. It is the opinion of the Canadian Multiple Organ Failure Study Group that the definitions of sepsis, sepsis syndrome and septic shock remain imprecise (210). The proposed definitions by Bone et al fail to differentiate between infection (a microbial phenomenon, with the invasion of sterile tissues by microorganisms) and the host response to infection, including hyper- or hypothermia, tachycardia, tachypnea, altered mental status, neutrophilia and increased cardiac output. Sibbald et al (210), therefore propose that " the central concept that should underlie a clarification of the terms ''infection'' and ''sepsis'' is the discrimination between phenomena that reflect effects of the microorganism and those that reflect the response of the host".

It is important to note that sepsis can result from other non infectious states e.g., pancreatitis and trauma, and that the hosts septic response is neither uniform in its response nor static in its progression. The term systemic inflammatory response syndrome (SIRS) has been proposed to describe the constellation of clinical manifestations which may be due to infectious and non infectious causes (211). Not all patients with severe infection may mount a septic response, particularly in the immunocompromised host.

The differentiation between infection and sepsis has therapeutic implications. Management of infection will include surgical debridement and appropriate antibiotic therapy, where as management of sepsis is directed at maintaining organ oxygenation and function using fluids or inotropes. The septic response may be a more important determinant of clinical outcome than invasive infection in critically ill patients (212).

Sepsis syndrome as defined by Dr Bone is therefore misleading in that it requires a suspicion of infection and the systemic response to it, and does not differentiate between the two.

Sepsis may result in a physiologic continuum of organ dysfunction with multiple organ failure being the end point. Therefore sepsis syndrome, septic shock, refractory septic shock and multiorgan failure represent stages of the physiologic continuum, that result from the hosts septic response. Sibbalt et al (210) having clearly distinguished between infection and the septic response, now call for consensus on the different stages and manifestations of sepsis.

Bearing in mind the limitations of the definitions proposed by Dr Bone, they are currently the most widely used definitions of sepsis, and were in use at the Baragwanath Hospital ICU at the time of this study. For this reason I have elected to utilise these definitions for the purpose of this thesis.

5.2 The Pathogenesis of sepsis.

The pathogenesis of the systemic response to inflammation is due to a complex cascade of molecular mediators including cytokines, prostanoids, and intermediates of oxygen metabolism. These substances are released from host cells, principally macrophages in addition to endothelial cells, neutrophils, platelets and lymphocytes in response to a variety of stimuli including infection, ischaemia, and the local release of mediators. The end result is severe endothelial damage, profound haemodynamic derangements, and often death (213,214,215,216,217).

5.2.1 The mediators of sepsis.

As a detailed description of the complex cascade of mediators of sepsis is beyond the scope of this thesis, an overview will be presented in diagrammatic form (Fig 11) (213).

As can be seen from fig 11, the initiating event is the release of endotoxin or comparable substances into the circulation. Endotoxin is a lipopolysaccharide component of the outer membrane of gram negative bacilli. Mononuclear phagocytes, endothelial cell and other cells are activated by circulating endotoxin to release tumour necrosis factor-alpha (TNF-α), interleukin-1,6 and 8 and platelet activating factor (PAF). TNF-α is thought to play a pivotal role in the pathogenesis of sepsis (218). Arachidonic acid metabolism is stimulated with the release of leukotrienes, thromboxane A_2 and prostaglandins and prostacycline (PGI_2). T cells are activated by interleukin 1 and 6 to produce interleukin 2 and 4, gama interferon and granulocyte monocyte colony stimulating factor (GM-CSF). The vascular endothelium is vulnerable to most of these factors, with resultant increase in endothelial permeability. Activation of complement results in hypotension and increased vascular permeability in addition to aggregation of neutrophils and platelets. Neutrophil induced damage may result from degranulation and release of toxic oxygen radicals, aggregation leading to microemboli formation and adherence to endothelium resulting in vasodilatation. Platelets may also induce endothelial damage by causing

vasoconstriction and neutrophil activation. Other factors known to be important in the sepsis cascade are adhesion molecules, kinins, factor XII, thrombin, beta endorphins, heat shock proteins and myocardial depressant factor.

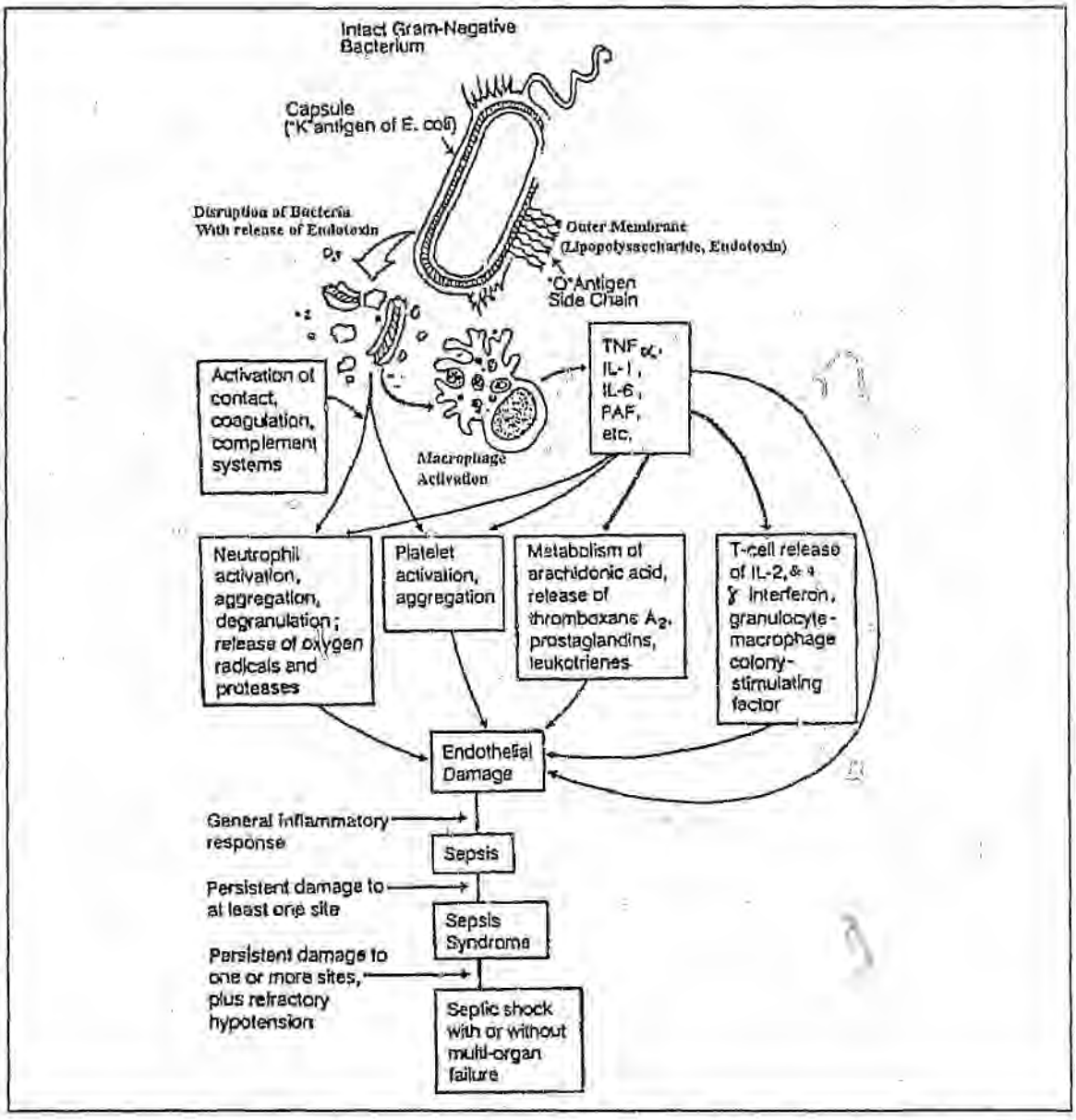


Fig 11: Schema of sepsis. Massive endothelial damage does not ordinarily occur because there are many points at which feedback loops down regulate mediator release. If the body cannot restore homeostasis, however, the generalized inflammatory response will produce clinical evidence of sepsis.

Homeostatic mechanisms for the down regulation of the sepsis cascade exist. Oxidative products may provide negative feedback to control inflammation. The ability of macrophages to release cytokines and other mediators may be dampend by the release of prostoglandin E_2, and T cell function may be suppressed by macrophages, thereby restoring homeostasis (213).

5.2.2 Endothelial dysfunction and haemodynamic mechanisms.

Endothelial function and dysfunction also play a central role in the development of septic shock and multiorgan failure. The endothelium produces endothelial-derived relaxing factor (EDRF) and endothelin-1, which oppose one another. EDRF causes vasodilatation and inhibits platelet aggregation, and endothelin-1 is a potent vasoconstrictor. The endothelium is also able to produce TNF-α, interleukin-1 and 6, PAF and arachidonic acid metabolites. The initial effects of the mediators released by the endothelium may be beneficial, if endothelial damage is repaired. If however, restoration of the endothelium does not occur, the inflammatory process will be perpetuated resulting in the continuous release of mediators into the circulation.
Microvascular insufficiency occurs due to vasoconstriction, vasodilatation, microembolization, and endothelial dysfunction resulting in uneven blood flow through capillaries, contributing to impaired oxygen utilisation.
Septic shock occurs once hypotension develops. The hypotension may result from the augmented release of EDRF and bradykinin, which reduce the systemic vascular resistance. Characteristically the cardiac output is increased at this stage. Regional increases in arteriovenous shunting occurs leading to tissue hypoxia. A decrease in the intravascular blood volume may occur due to an increase in microvascular permeability with the resultant loss of fluid into the interstitial space. Peripheral and hepatosplanchnic pooling markedly reduce venous return.
Myocardial dysfunction occurs early on in the development of sepsis and is purported to occur due to a myocardial depressant factor. Decreases in left ventricular stroke work and biventricular ejection fraction occur. Cardiac output is increased mainly due to an increased

heart rate. Cardiac dilitation occurs late in the course of sepsis.

Hyperlactaemia serves as an important marker of tissue hypoperfusion and hypoxia in septic shock. Oxygen extraction and utilization is impaired resulting in a flow dependent oxygen consumption, requiring higher than normal levels of oxygen delivery (219). Sepsis is characterised by a hypermeatabolic state, and persistant cellular hypoxia may become increasingly important in the late stages of sepsis when aerobic metabolism is impaired.

5.2.3 Multiple organ failure.(MOF)

MOF represents the terminal phases of the sepsis response, with a 80-100% mortality if three or more organs have failed (220). Whereas refractory hypotension is a main cause of early death, MOF is the primary cause of late deaths (221). An uncontrolled septic response, rather than uncontrolled infection, is suggested to be the most important pathogenic mechanism in MOF resulting in multiple sites of inflammation.

Respiratory failure due to the adult respiratory syndrome (ARDS) occurs in 30-80% of patients with septic shock (217).

Hepatic failure is frequently seen and may progress to liver failure. Renal insufficiency develops later and is due in part to intra-renal shunting, although hypoperfusion and nephrotoxic drugs contribute.

An alteration in intestinal epithelial function occurs in sepsis, due to ischemic mucosal injury, and results in increased permeability. Translocation of bacteria and bacterial toxin across the intestinal barrier fuel and perpetuate the systemic inflammatory response (222).

5.3 Management of sepsis.

Therapy is directed to optimising cardiac output and systemic oxygen delivery, through the use of fluid resuscitation and inotropic agents if necessary.

Down regulation of both cardiac and peripheral adrenergic receptors in septic shock may necessitate larger doses of inotropes, than are normally recommended, being used (223).

Appropriate antibiotic therapy has significantly improved survival. The use of high dose steroids has been shown to be of no benefit in the treatment of severe sepsis and septic shock (224,225).

Recently immunotherapy has come to the fore, in an attempt to manipulate the sepsis response. Monoclonal antibodies to endotoxin core glycoprotein are available. The administration of endotoxin antibody to patients with gram-negative bacteraemia has been demonstrated to cause early reversal of organ dysfunction and reduce mortality. Difficulty arises however in identifying accurately the subgroup which would respond to therapy with monoclonal endotoxin antibody. The use of monoclonal antibodies to TNF and interleukin-1, and the administration of interleukin-1 receptor antagonists and soluble receptors for TNF are currently under investigation (225,226).

6.0 Clinical Scoring systems in Sepsis.

Clinical scoring systems abound, and have been developed to meet specific clinical, research, or societal needs. Scoring systems have been in use for decades. The Glasgow Coma Scale and the APGAR score are well known examples. Scoring systems have been used to ensure quality control, cost containment, ensure appropriate resource utilization, and asses and compare new technological and therapeutic advances. The integration of scoring systems into every day clinical life will be determined by their validity, practicality and physician acceptance.

The ideal scoring system should be characterised by the following properties (227),

(i) data should be readily obtainable and easy to compute

(ii) and be, reproducible over time, and should include the following variables,

- disease e.g., trauma, sepsis.
- Anatomic factors e.g., Liver, kidney.
- predisposing factors e.g., age, heart disease.
- physiological parameters e.g., vital signs
- disease/patient factors e.g., nutritional and immunological status.

A number of scoring systems meet these criteria and allow for comparison of patients in different institutions and provides a common basis for multi institutional studies. However the ability to predict outcome and risk for the individual patient is not possible due to difficulties in methodology, and the effect of therapeutic intervention on outcome.

A lack of understanding of the pathophysiologic mechanisms of sepsis and its complications has lead to the development of numerous scoring systems. (see table 2)(228)

- Septic Severity Score
- Sepsis Score
- Sepsis Index of Survival
- Theraeutic Intervention Scoring System (TISS)
- Acute Physiological assessment (APS-34)
- Multiple System Severity of Illness Score (MSIS)
- Acute Physiology and Chronic Health Evaluation (APACHE II, APACHE III)

Table 2: Scoring systems used for septic patients.

As the APACHE II was the only scoring system used in this research, I will confine my discussion to it.

The APACHE II scoring system devised by Knaus et al (229), evolved from their prototype APACHE scoring system (107). The APACHE was designed as a severity of disease classification using acute physiologic measurements. The original APACHE uses 34 physiologic measures, the sum of which yields an acute physiologic score (107). The APACHE II uses 12 physiologic variables all of which are weighted, based on a score of 0-4 (Table 3) (229).

Table 3. The APACHE II severity of disease classification system.

PHYSIOLOGIC VARIABLE	HIGH ABNORMAL RANGE					LOW ABNORMAL RANGE			
	+4	+3	+2	+1	0	+1	+2	+3	+4
TEMPERATURE*— rectal (°C)	≥41°	39°-40.9°		38.5°-38.9°	36°-38.4°	34°-35.9°	32°-33.9°	30°-31.9°	≤29.9°
MEAN ARTERIAL PRESSURE — mm Hg	≥160	130-159	110-129		70-109		50-69		≤49
HEART RATE (ventricular response)	≥180	140-179	110-139		70-109		55-69	40-54	≤39
RESPIRATORY RATE — (non-ventilated or ventilated)	≥50	35-49		25-34	12-24	10-11	6-9		≤5
OXYGENATION: A-aDO$_2$ or PaO$_2$ (mm Hg) a. FIO$_2$ ≥0.5 record A-aDO$_2$	≥500	350-499	200-349		<200				
b. FIO$_2$ <0.5 record only PaO$_2$					PO$_2$ > 70	PO$_2$ 61-70		PO$_2$ 55-60	PO$_2$ <55
ARTERIAL pH	≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	< 7.15
SERUM SODIUM (mMol/L)	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110
SERUM POTASSIUM (mMol/L)	≥7	6-6.9		5.5-5.9	3.5-5.4	3.0-3.4	2.5-2.9		<2.5
SERUM CREATININE (mg/100 ml) (Double point score for acute renal failure)	≥3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6		
HEMATOCRIT (%)	≥60		50-59.9	46-49.9	30-45.9		20-29.9		<20
WHITE BLOOD COUNT (total/cmm3) (in 1,000s)	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1
GLASGOW COMA SCORE (GCS): Score = 15 minus actual GCS									
[A] Total ACUTE PHYSIOLOGY SCORE (APS): Sum of the 12 individual variable points									
Serum HCO$_3$ (venous) mMol/L (Not preferred, use if no ABGs)	≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15

[B] AGE POINTS:
Assign points to age as follows:

AGE (yrs)	Points
≤44	0
45-54	2
55-64	3
65-74	5
≥75	6

[C] CHRONIC HEALTH POINTS
If the patient has a history of severe organ system insufficiency or is immuno-compromised assign points as follows:

a. for nonoperative or emergency postoperative patients — 5 points
or
b. for elective postoperative patients — 2 points

DEFINITIONS
Organ insufficiency or immuno-compromised state *must have been evident prior* to this hospital admission and conform to the following criteria:

LIVER: Biopsy proven cirrhosis and documented portal hypertension; episodes of past upper GI bleeding attributed to portal hypertension, or prior episodes of hepatic failure/encephalopathy/coma.

CARDIOVASCULAR: New York Heart Association Class IV.

RESPIRATORY: Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction, i.e., unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40mmHg), or respirator dependency.

RENAL: Receiving chronic dialysis.

IMMUNO-COMPROMISED: The patient has received therapy that suppresses resistance to infection, e.g., immuno-suppression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, e.g., leukemia, lymphoma, AIDS.

APACHE II SCORE

Sum of [A] + [B] + [C] =

[A] APS points _____

[B] Age points _____

[C] Chronic Health points _____

Total APACHE II _____

The following physiologic variables are measured:

* Sepsis
  - temperature
* Cardiovascular
  - mean arterial pressure
  - heart rate
  - arterial pH
* Respiration
  - respiratory rate
  - oxygenation $P(A\text{-}a)O_2$ (100%) or PaO_2
* Metabolic
  - serum sodium
  - serum potassium
  - Bicarbonate (if arterial blood gas not done)
* Renal
  - creatinine
* Haematological
  - haematocrit
  - white blood cell count
* Neurological
  - Glasgow Coma Score

The worst measurement for each physiologic variable in the first 24 hours is recorded. Because age and severe chronic disease are independent risk factors for death in acute illness, both have been directly incorporated into APACHE II. As can be seen from Table 3 only severe chronic illnesses have been included. In addition patients who are nonoperative or emergency operative admissions with severe chronic organ system dysfunction are weighted more heavily. The maximum possible APACHE II score is 71.

Figure 12 demonstrates the relationship between the APACHE II score and mortality rate as demonstrated by Knause et al (229). That is, as the APACHE II score increased so did the mortality rate, and a score of 35+ was associated with a mortality rate of greater than 80%.

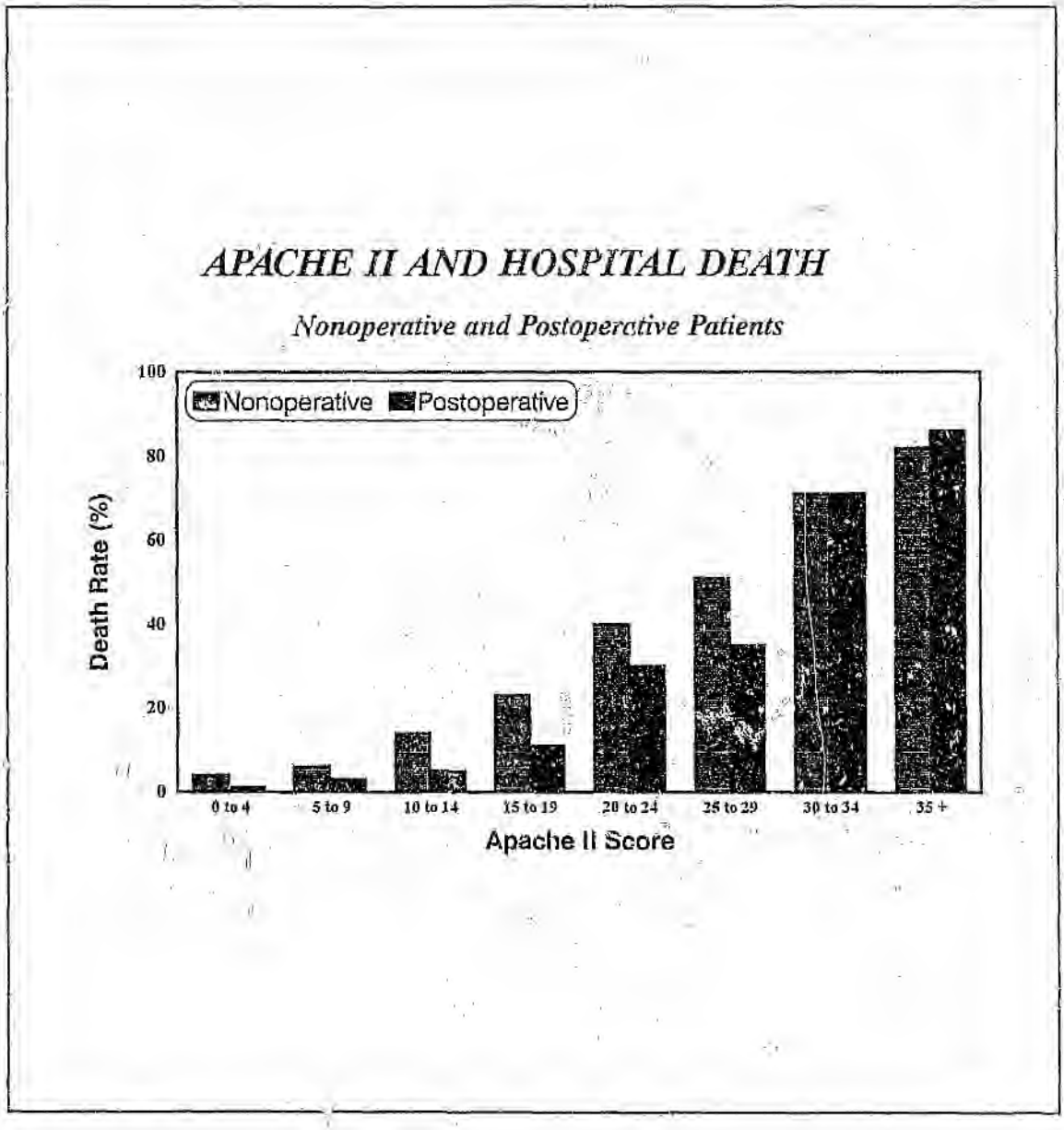


Fig 12: Apache II vs Mortality

It is of interest that in Knaus's series there was an excess mortality in patients with septic shock and an APACHE II score between 0-9, in which there were 6 patients and 2 deaths (Fig 13). However the APACHE II score has been validated as a useful prognostic tool in sepsis (230). The APACHE II score has been used as the risk stratification method in clinical studies of severe infection such as necrotizing fasciitis, pancreatitis, intraabdominal abscess and peritonitis (228).

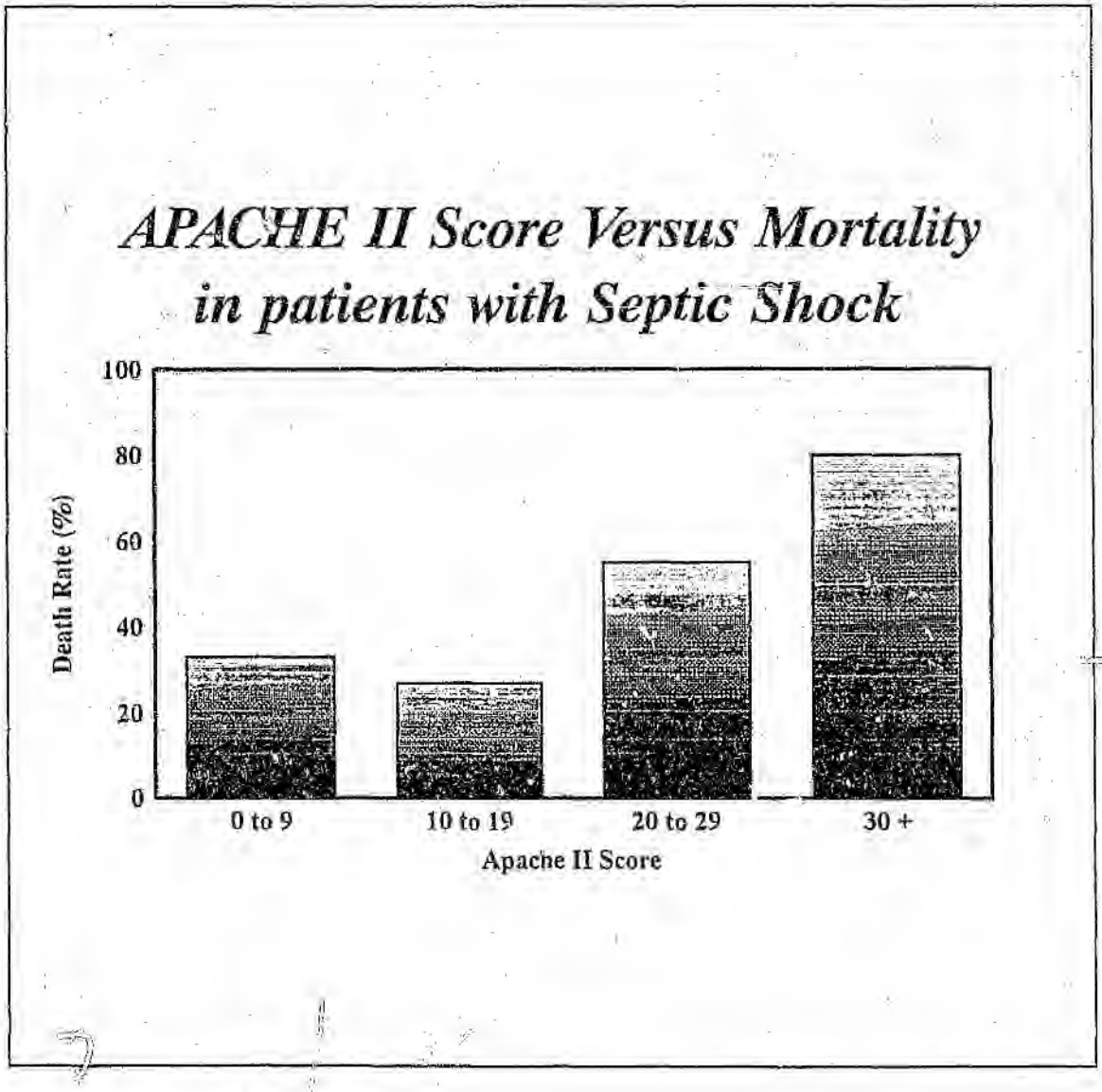


Fig 13: Apache II vs Septic shock.

It is also possible to calculate the predicted death rate for acutely ill groups of patients by combining the APACHE II score with a precise description of disease. Individual diagnostic categories are allocated coefficients which are then incorporated into a formula with the APACHE II score to compute the estimated risk of hospital death.

Certain reservations and limitations of the APACHE II scoring system have been expressed. The validity of the APACHE II score to predict mortality and as a quality control tool in trauma and postoperative patients has been questioned by recent studies (228). The static nature of the APACHE II score has been severely criticised. Some authors have calculated the APACHE II score on a daily basis, instead of on admission only, in order to provide a trend analysis. Chang et al (231) did daily APACHE II scores on 310 consecutive adult intensive care patients. Organ failure sores were derived from the APACHE II score by applying a coefficient which corresponded to the number and duration of organ failures. The analysis took into account the absolute value of the daily scores and the rate of change relative to the previous day. The predictive power of daily organ failure scores was superior to those obtained from a single APACHE II score or from daily APACHE II scores by a factor of 5.3 and 1.4 respectively. Coppa et al (228) in the surgical ICU at Bellevue Hospital found that daily trend analysis correlated more precisely with outcome than did individual scores.

In conclusion therefore scoring systems can not replace sound clinical acumen but can aid in the decision making.

PART II

THE RELATIONSHIP BETWEEN CHANGES IN CRITICALLY ILL SEPTIC AND NON SEPTIC PATIENTS AND CIRCULATING THYROXINE LEVELS.

7.0 Research:

7.1 INTRODUCTION.

Articles pertaining to alterations in thyroid hormone levels in non thyroid illness, particularly in the critically ill, abound. Clinical assessment of thyroid status in critically ill patients is notoriously difficult. In the critically ill, signs may mimic or mask signs of thyroid disease, in that patients are frequently catabolic, tachycardic, pyrexial or hypothermic.

Biochemical assessment of the thyroid status in this group of patients is also difficult. Although the patient is clinically euthyroid, the alterations in thyroid hormone levels would tend to suggest hypothyroidism. Perturbations in thyroid hormone economy in critically ill patients occur not only due to changes produced by NTI, but also due to drugs commonly used in the ICU. Dopamine, heparin and corticosteroids being the commonest drugs used in ICU that may alter thyroid hormone levels. Malnutrition may also contribute to the observed changes in thyroid hormone levels. Critically ill patients frequently have hepatic and renal impairment. As these organs are the major sites of T4 degradation (76), this too may contribute to the observed changes in thyroid hormone levels in the critically ill. Hoffman et al (232) conclude that 50% of the low values, in thyroid function tests in critically ill patients, may represent inaccuracies of the thyroid hormone assays. Alterations in thyroid hormone levels have been linked to duration (98,99), severity of illness and outcome (105).

Boles et al (49) have quantified the severity of illness using the APACHE II score and associated this with the reduction in TT4. Arregui et al (230) have validated the APACHE II score as a useful prognostic tool in sepsis.

Although numerous articles exist dealing with infections and their effect on thyroid hormone economy, few exist pertaining to the bodies systemic response to infection (septic syndrome, septic shock and multiple organ dysfunction) and alterations in thyroid hormone levels.

The aim of this study is to;

1) Document the severity of the euthyroid sick syndrome at resentation in critically ill septic and non septic patients.

2) Monitor and relate the clinical progress of the patients to changes in circulating thyroxine levels.

3) Correlate serum thyroxine measurements, as a prognostic indicator, to outcome.

7.2 Patients and methods.

7.2.1 Patient Selection.

Patients admitted to the Baragwanath Hospital Intensive Care Unit were studied over a period of six months. Optimal ICU treatment was provided to all patients. Adult medical, surgical and gynaecological patients admitted to the ICU were assessed clinically and, if they met the inclusion criteria, assigned to one of the following categories;

i) Non septic i.e., no clinical evidence of infection.
Prophylactic use of antibiotics did not exclude the patient from being classified as non septic.

ii) Septic syndrome, as defined by Bone et al. (202,204,205,Chapter 5.1).

iii) Septic shock, as defined by Bone et al. (202,204,205,Chapter 5.1).

The following patients were excluded from the study. Those who were less than 18 years or older than 75 years of age, with known thyroid disease, on thyroxine treatment, and patients with known or suspected hypothalamic or pituitary disease or head trauma.
Verbal consent was obtained where possible from the patient or family. The study was accepted by the Committee for Research on human subjects of the University of the Witwatersrand.

7.2.2 Patient Data.

Details of patients studied are presented in Table 4, 5, and 6.

	(n)	Mean Age	SD
1) Non septic.	15	42	19.4
2) Septic Syndrome	25	34.6	14.7
3) Septic Shock	8	40.6	13.6

Table 4. Non-Septic Patients.

Study Number	Sex	Age	Diagnosis	ICU Days	Outcome: Alive/dead
A01	M	50	Asthma, cardiomyopathy	36	Alive
A02	F	74	Asthma	4	Alive
A03	F	22	Asthma	3	Alive
A04	M	32	Aneurysm surgery	2	Alive
A05	M	44	Anaphylaxis, CRF	2	Alive
A06	F	30	Eaton Lambert Syndrome	16	Alive
A07	F	67	Myocardial infarct,H/T, NIDDM	3	Alive
A08	F	21	Post partum CMO	14	Alive
A10	M	21	Malignant H/T, ARF	4	Alive
A11	M	72	Myocardial Infarct	4	Alive
A12	F	21	H/T, CRF	3	Alive
A13	M	57	Carcinoma oesophagus Post Oesophagectomy	12	Alive
A14	F	60	Myocardial infarct	8	Alive
A15	M	40	Myocardial infarct	4	
A16	M	19	Orthopaedic surgery	11	Alive

A09 was omitted because the inflammatory response syndrome (septic syndrome) of pancreatitis can not be differentiated from that due to infection.

Table 5. Septic Syndrome Patients.

Study Number	sex	Age	Diagnosis	ICU Days	Outcome Alive/dead
B01	M	21	Severe Pneumonia	3	Dead
B02	M	32	Perforated DU, Hosp. Pneumonia	20	Alive
B03	F	27	Comm. Pneumonia	12	Alive
B04	F	18	Asthma, Comm. Pneumonia	4	Alive
B05	F	44	Gynaecological sepsis	4	Alive
B06	F	25	Gynaecological sepsis	4	Dead
B07	F	33	Comm. Pneumonia	20	Alive
B08	M	21	Abdominal sepsis	17	Alive
B09	M	51	Abdominal sepsis	19	Alive
B10	M	35	Comm. Pneumonia	32	Dead
B11	F	26	Gynaecological sepsis	8	Alive
B12	M	25	Comm. Pneumonia	3	Alive
B13	F	20	Gynaecological sepsis	12	Alive
B14	M	24	Comm. Pneumonia	3	Alive
B15	M	29	Thoraco-abdominal sepsis	9	Dead
B16	M	20	Cardiomyopathy Comm. Pneumonia	10	Dead
B17	M	30	Comm. Pneumonia Meningitis	14	Alive
B18	M	39	Comm. Pneumonia	4	Alive
B19	F	60	Abdominal sepsis	7	Dead
B20	F	45	Comm. Pneumonia	4	Alive
B21	M	68	Comm. Pneumonia	3	Dead
B22	M	74	Comm. Pneumonia	2	Dead
B23	F	33	Hosp. Pneumonia	12	Dead
B24	M	36	Comm. Pneumonia	18	Dead
B25	F	24	Gynaecological Sepsis	18	Alive

Table 5. Septic Syndrome Patients.

Study Number	sex	Age	Diagnosis	ICU Days	Outcome Alive/dead
B01	M	21	Severe Pneumonia	3	Dead
B02	M	32	Perforated DU, Hosp. Pneumonia	20	Alive
B03	F	27	Comm. Pneumonia	12	Alive
B04	F	18	Asthma, Comm. Pneumonia	4	Alive
B05	F	44	Gynaecological sepsis	4	Alive
B06	F	25	Gynaecological sepsis	4	Dead
B07	F	33	Comm. Pneumonia	20	Alive
B08	M	21	Abdominal sepsis	17	Alive
B09	M	51	Abdominal sepsis	19	Alive
B10	M	35	Comm. Pneumonia	32	Dead
B11	F	26	Gynaecological sepsis	8	Alive
B12	M	25	Comm. Pneumonia	3	Alive
B13	F	20	Gynaecological sepsis	12	Alive
B14	M	29	Comm. Pneumonia	3	Alive
B15	M	29	Thoraco-abdominal sepsis	9	Dead
B16	M	20	Cardiomyopathy Comm. Pneumonia	10	Dead
B17	M	30	Comm. Pneumonia Meningitis	14	Alive
B18	M	39	Comm. Pneumonia	4	Alive
B19	F	60	Abdominal sepsis	7	Dead
B20	F	45	Comm. Pneumonia	4	Alive
B21	M	68	Comm. Pneumonia	3	Dead
B22	M	74	Comm. Pneumonia	2	Dead
B23	F	33	Hosp. Pneumonia	12	Dead
B24	M	36	Comm. Pneumonia	18	Dead
B25	F	24	Gynaecological Sepsis	18	Alive

Table 6. Septic Shock Patients.

Study Number	Sex	Age	Diagnosis	ICU Days	Outcome Alive/Dead
C02	F	38	Septic abortion	44	Dead
C03	M	45	Diabetes, Comm. Pneumonia	8	Alive
C04	F	32	Septic abortion	2	Dead
C05	F	24	Septic abortion	2	Dead
C06	M	68	Comm. Pneumonia	3	Dead
C07	F	35	Comm. Pneumonia	1	Dead
C08	F	54	Comm. Pneumonia	11	Alive
C09	F	29	Gynaecological sepsis	8	Dead

C01 was excluded due to biochemical evidence of hypothyroidism, i.e., a TSH level > 5.5uIU/ml.

The following data was also recorded:

- Major diagnosis and other clinical problems.
- Indications for surgery.
- Vital signs and clinical assessment for APACHE II score.
- Drugs administered to the patient.
- Outcome.

7.2.3 Special Investigations.

The following routine investigations were done on admission

- Arterial blood gas
- Full blood count
- Urea, sodium, potassium, chloride, total carbon dioxide, creatinine.
- sepsis work up where clinically indicated.
- Chest radiograph and electrocardiograph
- APACHE II Score as defined by Knaus et al (229) (see Chapter 6).

At the same time an additional 10 mls of blood was taken for

- Total triiodothyronine (TT3)
- Total thyroxine (TT4)
- Thyrotropin stimulating hormone (TSH)
- Thyroxine binding globulin (TBG)

The blood samples for thyroid function studies were immediately centrifuged and the sera stored at - 20°c until assayed.

Patients assigned to the septic syndrome group were followed prospectively and serial serum TT4 levels were done three times weekly, at the same time as routine venesection, for up to three weeks depending on outcome. If the patients clinical condition progressed from one category to another, full thyroid function tests were repeated.

Reference values were established using twenty three black, age and sex matched healthy blood donors. There were eleven males and twelve females.

Radioimmunoassay.

The serum TT3 and TT4 were assayed using the Amerlex-M radioimmunoassay kit, Amerlite Diagnostics (LTD), Amersham, England.

Methodology:

Thyroxine is liberated from carrier proteins with 8 anilino-1-naphthalenesulfonic acid. Patients serum is added to tubes coated with T4 antibody. Radiolabelled T4 tracer is added and the solution incubated for 45 minutes at room temperature. The supernatant is poured off and discarded. The radioactivity of the antibody-bound hormone, which is on the wall of the tubes,

is counted. A standard curve is plotted from which the T4 concentration is determined. All assays were analyzed in duplicate according to the manufacturers instructions.
The assay for TT3 is similar.

Quality Control:

Commercial quality control serum (Amersham) was used to ensure results with in acceptable limits were obtained.

Precision:

Intra-assay reproducibility was assessed using control sera. The coefficients of variation (CV)

* TT4 = 1-8.4%

* TT3 = 2-3.6%

Reference Range:

A reference range was determined in a population of healthy blood donors. Total thyroxine levels ranged from 35.5-117.5 nmol/L (mean = 76.5; SD = 17.3). The manufactures report a normal range of 62-165nmol/L. Total triiodothyronine levels ranged from 0.8-1.9 nmol/L. (mean = 1.3; SD = 0.3). The manufactures reported normal range is 0.8-2.7.

Thyroxine Binding Globulin.

Thyroxine Binding Globulin (TBG) was measured by radioimmunoassay (RIA), using the TBG RIA kit (CIS bio international, France).

Methodology:

The assay is based on competition between iodine 125 labelled TBG, and TBG contained in standards or in the specimen to be assayed, for a fixed and limited number of antibody binding sites. The assay involves a single incubation for the competition and separation steps. At the

end of the incubation the amount of labelled TBG bound to antibody is inversely related to the amount of unlabelled TBG present in the assay.

Quality Control:

Control sera supplied by the manufacturer were used to insure that results obtained were within acceptable limits.

Precision:

The coefficients of variation for intra-assay reproducibility were

* control 1 = 2.2%
* control 2 = 4.1%

Reference Range:

Healthy blood donors were used as controls. TBG levels ranged from 6.1-31.6 μg/ml (mean = 19.1, SD = 6.0). Manufacturers reported values are; mean = 20.5μg/ml, SD = 4.07μg/ml.

Thyrotropin.

The Amerlex-M TSH RIA kit was used.

Methodology:

The RIA method depends on the competition for a limited number of binding sites on a TSH-specific antibody between TSH in serum and ^{125}I-labeled TSH. The proportion of ^{125}I-labeled TSH bound to antibody is inversely related to the concentration of TSH present in serum. The antibody bound TSH is then reacted with the Amerlex-M second antibody reagent which contains magnetisable polymer particles coated with solids from donkey anti-rabbit antibody. Separation of the antibody-bound fraction is effected by magnetic separation of the Amerlex-M

suspension and decantation of the supernatant. By measuring the proportion of ^{125}I-labeled TSH bound in the presence of reference standard solutions containing known amounts of TSH, the concentration of TSH present in the unknown samples can be interpolated.

Quality Control:

To ensure that results obtained were within acceptable limits, commercially supplied control sera were used.

Precision:

The coefficients of variation for intra-assay reproducibility were

* control 1 = 2.4%
* control 2 = 2.3%

Reference Range:

The reference range using healthy blood donors was 0.8-3.2μIU/ml (mean = 1.8, SD = 0.6). The manufactures values ranged from 1.0-5.5μIU/ml.

Free Thyroxine and Triiodothyronine.

Free thyroxine and triiodothyronine were not done as part of this study due to limitation of finances. It would however have been desirable to include FT4 and FT3 in order to gain a fuller understanding of the perturbations that occur in the euthyroid sick syndrome. The free thyroxine concentration may be evaluated using the values of total thyroxine and thyroid binding globulin by applying the Lecureuil formula (233).

The T4:TBG ratio as proposed by Burr (234) may also be used.

As stated previously, the T4:TBG ratio correlates with the FTI and FT4 for simple thyroid disease and euthyroidism without NTI (190). Cognisance however should be taken of the data from Slag et al.(235) which demonstrates a correlation between T4:TBG ratio and free T4 by

equilibrium dialysis of only 0.61. However if the T4:TBG ratio or the direct measurements of free T4 are used alone in the assessment of thyroid function in critically ill patients, hypothyroidism would be suspected in a large proportion of patients. The range of results for the T4:TBG ratio in healthy blood donors was 2.1-8.9 (Mean = 4.0, SD = 1.8). The T4:TBG ratio was used in this study as a measure of free thyroxine.

7.2.4 Statistical Analysis.

Data was analyzed by analysis of variance (Kruskal Wallis), Chi-Square test and Spearman correlation coefficient as indicated in the text.

Results for parametric data are expressed as the mean $\pm$ SD.

Results for non-parametric data are expressed as the median and the range.

Statistical analysis was done in consultation with the Biostatistics Department, University of the Witwatersrand.

8.0 RESULTS.

Raw data can be found in appendix 1, 2 & 3.

Results will be divided according to a) Admission data

b) Trends analysis

8.1 Admission Data.

On admission to the ICU, blood for TT4, TT3, TBG, and TSH was done on all patients allocated to the non septic (N/S), septic syndrome (S/SYN), and septic shock (S/S) groups. An APACHE II score was recorded after the first 24 hours of admission.

8.1.1 Sepsis versus Non Sepsis.

Details of the patient sub groups for the various thyroid hormone assays are shown in Table 7. The frequency histogram for TT3 (figure 14a) and TSH (figure14b) demonstrate the non parametric nature of the data, in contrast to TT4 and TBG. The findings for TT3 are in keeping with what is expected from the euthyroid sick syndrome (ESS) in non thyroidal illness, i.e., low T3 values being the commonest finding in the ESS.

Table 7. Sepsis vs thyroid function tests, mortality and APACHE II score. SD in parenthesis, range given for non-parametric data

	n	TBG µg/ml	TSH µIU/ml	TT3 nmol/L	TT4 nmol/L	MORTALITY(%)	APACHE
Ref. Range		12.4-28.6	1.0-5.5	0.8-2.7	62-165		
Control	23	19.1 (6.0)	1.8 (0.6)	1.3 (0.3)	76.5 (17.3)		
N/S	15	18.4 (5.9)	2.1 .7-3.7	0.9 .2-1.6	65.2 (19.9)	0	11.5 (6.2)
S/SYN	25	15.5 (5.7)	1.4 .7-5.6	0.3 .1-1.4	52.4 (22.7)	40	14.9 (5.6)
S/S	8	12.3 (5.9)	1.5 .6-5.1	0.3 .1-0.8	42.7 (25.5)	75	22.3 (6.4)
p-value		0.04	0.46	0.001	0.05	0.001	0.005

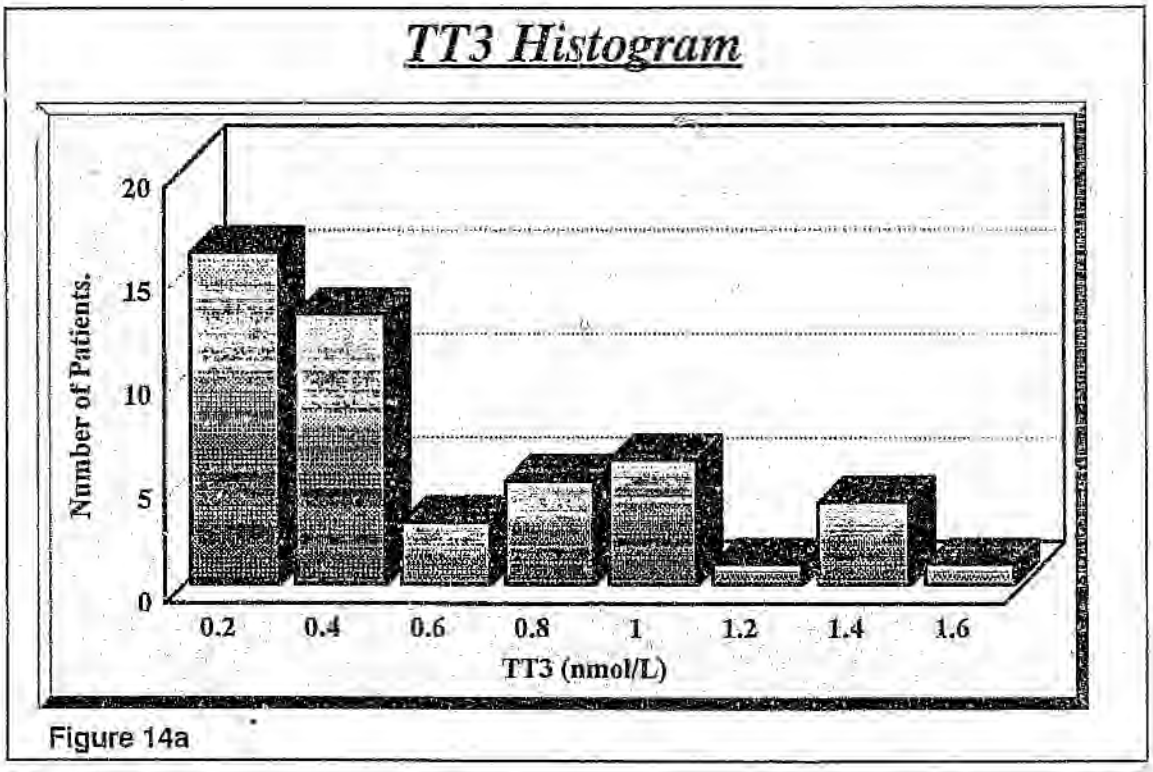


Figure 14a

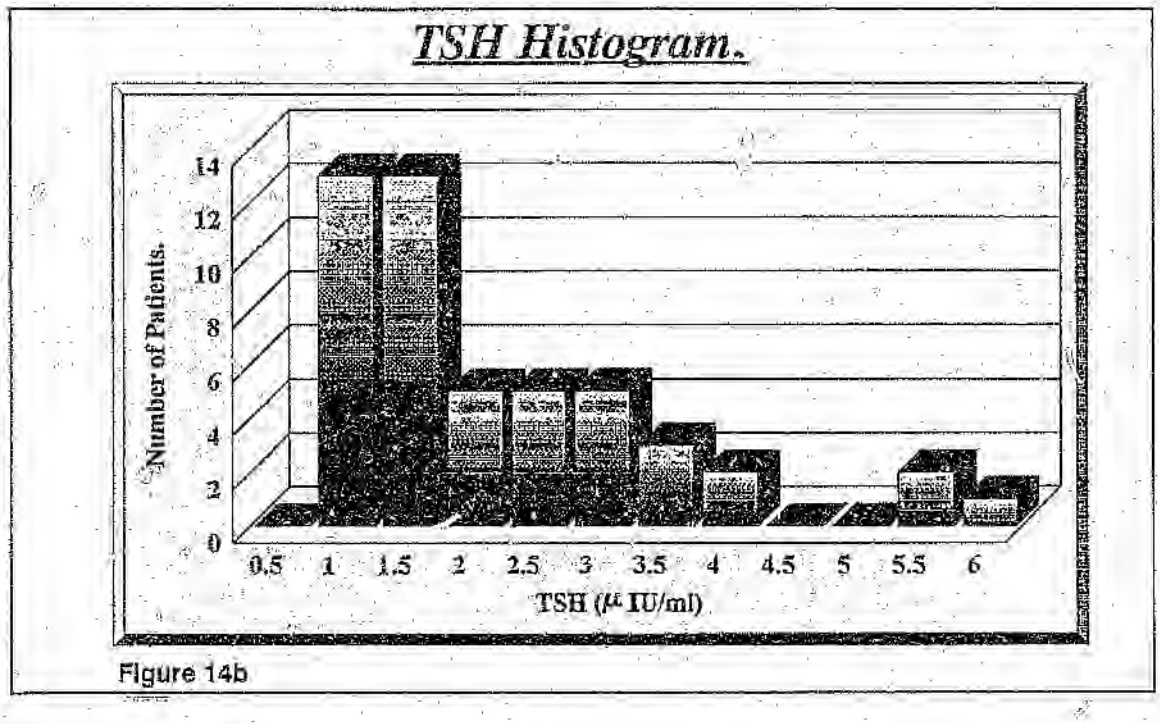


Figure 14b

Figure 15(a,b,c). demonstrates the relationship between sepsis (N/S, S/SYN, S/S) and mortality, TT4, TT3, TBG and APACHE score.

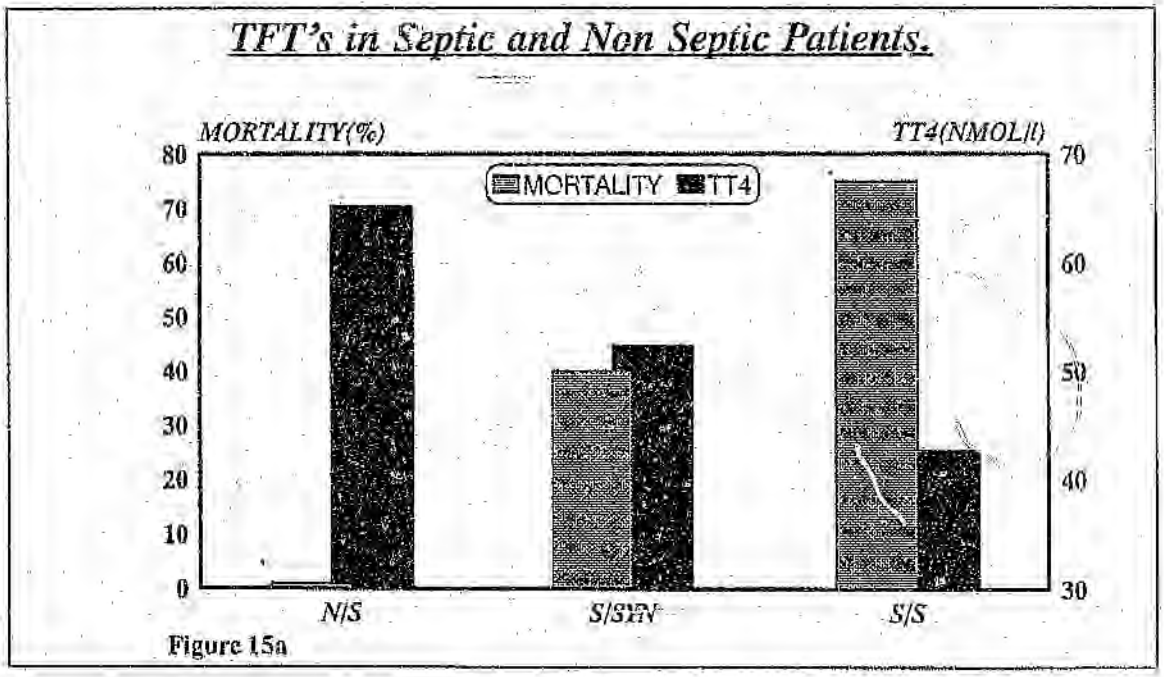


Figure 15a

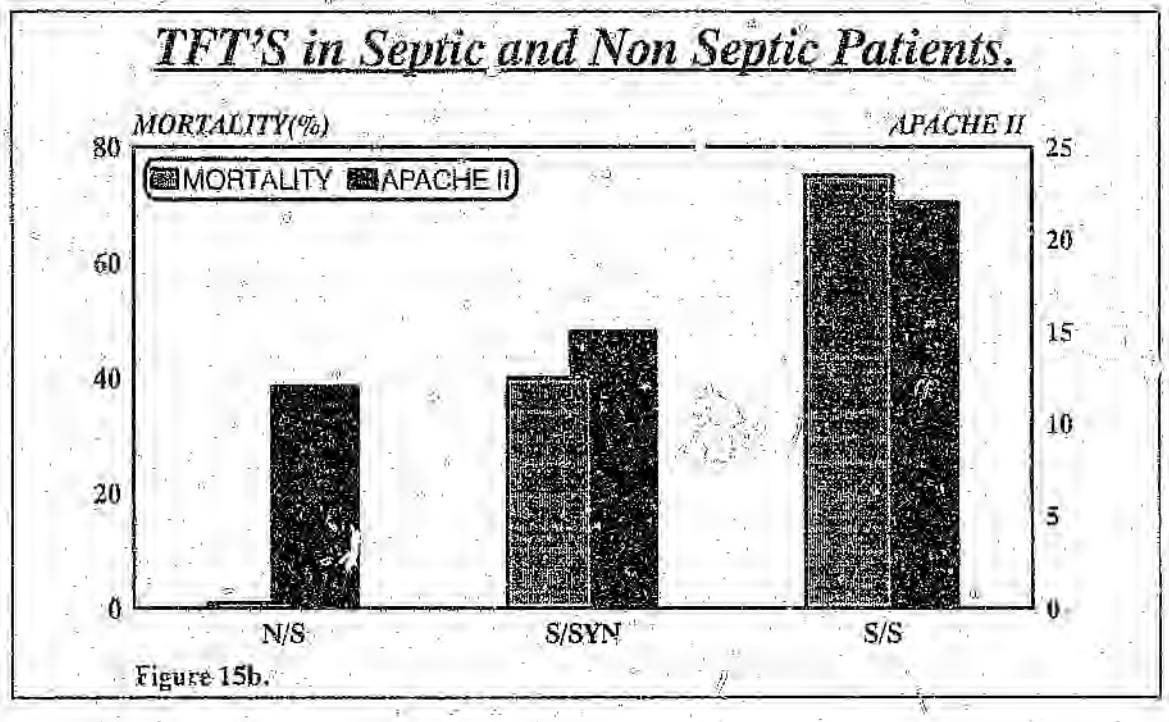


Figure 15b.

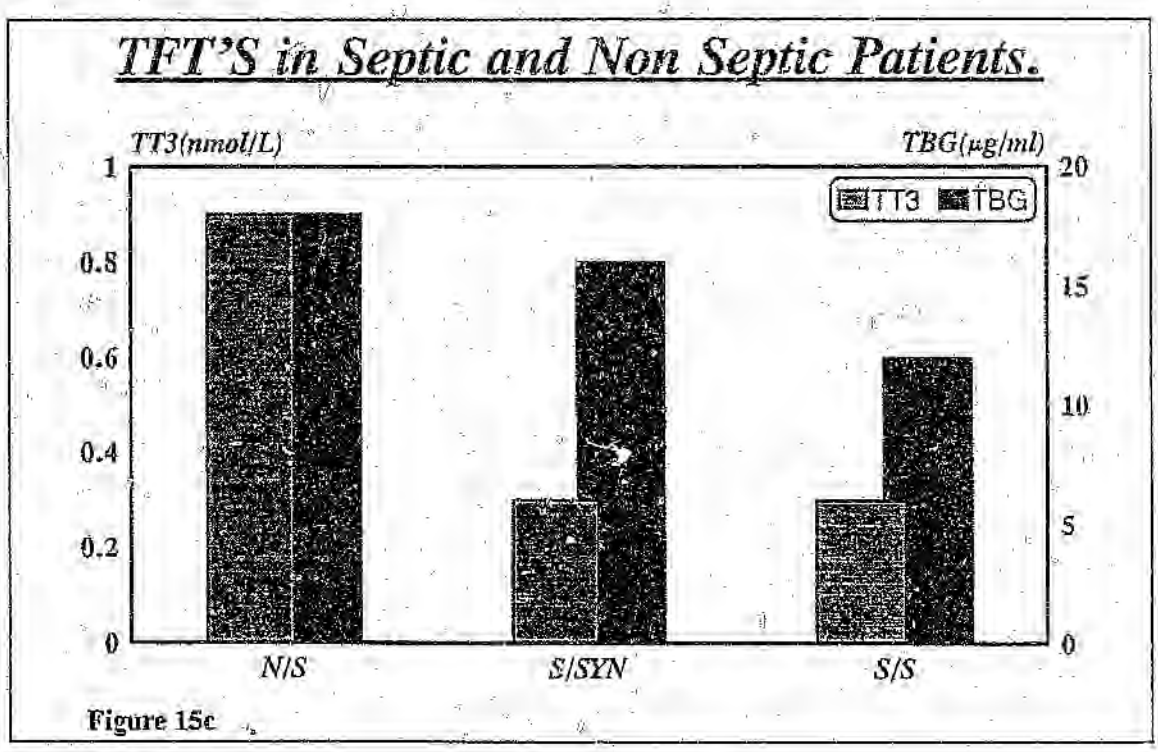


Figure 15c

When comparing results between the N/S, S/SYN, S/S groups (Table 7, Figure15a,b,c) there was a significant difference between the TT3 ($p=0.001$), TBG ($p=0.04$), mortality (Chi-Square = 14.3, $p=0.001$) and APACHE score ($p=0.005$). Serum TT4, TT3 and TBG decreased, and the APACHE and mortality increased as the degree of sepsis increased (Figure 15a,b,c). A mortality rate of 75% in patients with septic shock is in keeping with published data (204). The difference between the TT4 was just significant ($p=0.05$), and the difference between TSH was not significant. Of interest to note is that the only difference between the control group and patients who were non septic was a lower serum TT3 level in the N/S group ($p=0.004$), in keeping with the low T3 syndrome.

The TT4:TBG ratio for the N/S, S/SYN, S/S groups were 3.9, 3.6, and 3.3 respectively. Although there was a downward trend, there was no significant deference between the three groups.

Thyroid binding globulin like albumin is produced in the liver, and both are altered in NTI. Thirty four patients on admission had both TBG and albumin results available. A correlation analysis between TBG and albumin revealed a significant correlation ($r=0.62$, $p=0.0001$).

The impact of sepsis on thyroid function tests was assessed by comparing patients in the non septic and septic syndrome groups with a similar severity of illness (APACHE < 20) (Table 8).

Table 8. Septic and Non Septic Patients with a similar severity of illness. SD in parenthesis. Range given for non-parametric data.

	n	TSH μIU/ml	TBG μg/ml	TT3 nmol/L	TT4 nmol/L	MORT
N/S	14	2.2 0.7-3.7	18.5 (6.1)	0.9 0.2-1.6	67.7 (18)	0
S/SYN	20	1.35 0.7-3.3	16.1 (6.0)	0.3 0.1-1.4	56 (23.5)	30
p value		0.09	0.25	0.001	0.12	0.02

Only a significant difference exists with TT3 and mortality. This suggests that sepsis may worsen the prognosis and result in greater perturbations in thyroid hormone levels.

8.1.2 Correlation of Admission Data.

The admission data for all three groups (N/S, S/SYN, S/S) were pooled and a correlation analysis performed (Table 9).

Table 9. Spearman correlation between thyroid function tests and APACHE score.

	APACHE	TT3	TT4	TSH	TBG
APACHE	1.0 0.0				
TT3	-0.52 0.0001	1.0 0.0			
TT4	-0.46 0.003	0.83 0.0001	1.0 0.0		
TSH	0.03 0.7	0.08 0.86	-0.13 0.24	1.0 0.0	
TBG	-0.35 0.02	0.7 0.0001	0.73 0.0001	-0.08 0.37	1.0 0.0

Upper value represents R (Spearman).
Lower value represents p-value.

Strong significant positive correlations exists between TT4, TT3 and TBG. The APACHE II score correlates significantly with TT3, but less so with TT4. Thyrotropin does not correlate with any of the other values.

8.1.3 Serum Total Thyroxine.

Figure 16. demonstrates the relationship between serum TT4 and APACHE, TT3, TBG and mortality.

The admission serum TT4 were divided into three groups, i.e., TT4 greater than 60 nmol/L (ie. normal), between 40-60 nmol/L (mild-moderately depressed), and less than 40 nmol/L (severely depressed).

TT4(nmol/L) (n=62-165)	n	Mean
>60	19	79
40-60	15	48
<40	14	28

As the serum TT4 level decreased there was a significant decreases in serum TT3 ($p<0.0001$) and TBG ($p<0.0001$) levels. This is in keeping with the low T3 and low T3,low T4 syndromes reported. The decrease in TBG can only partly explain the decrease in TT4 levels.

Although the APACHE II score increased significantly between the three groups ($p=0.02$) there was no difference in APACHE II score between the first two groups. This would tend to suggest that the severity of illness between the first two groups was similar. However the mortality rate increased significantly between the first two and all three groups respectively (Chi-Square=7.0, $p=0.03$).

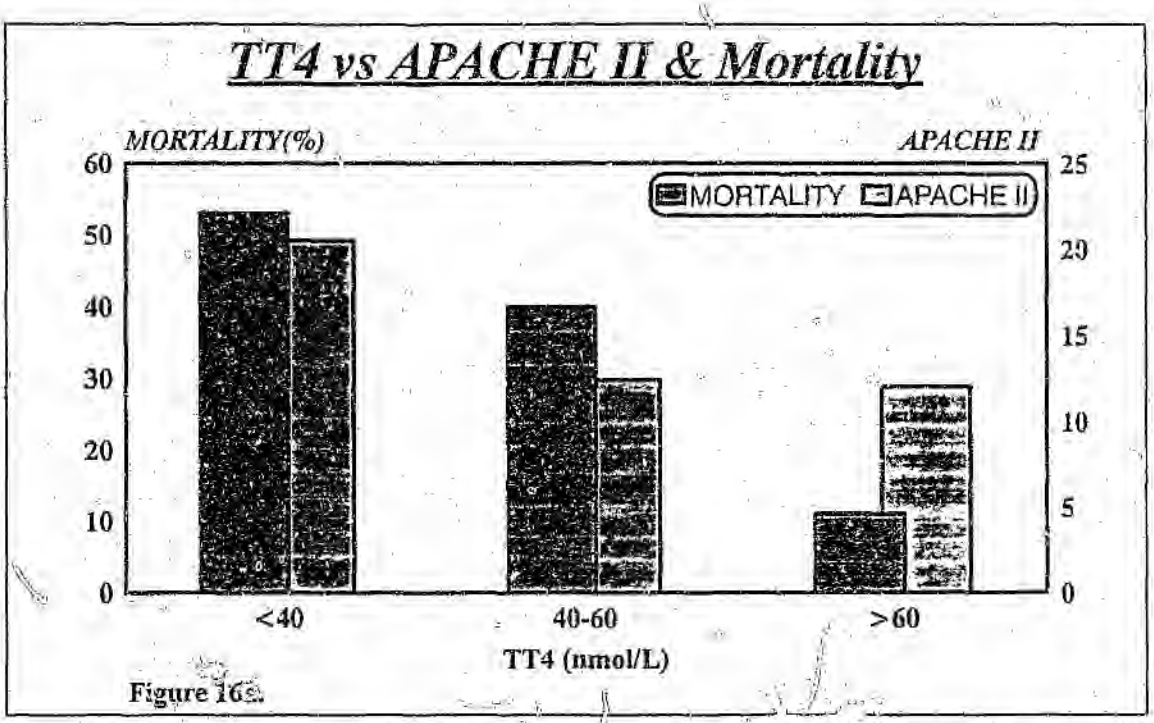


Figure 16a.

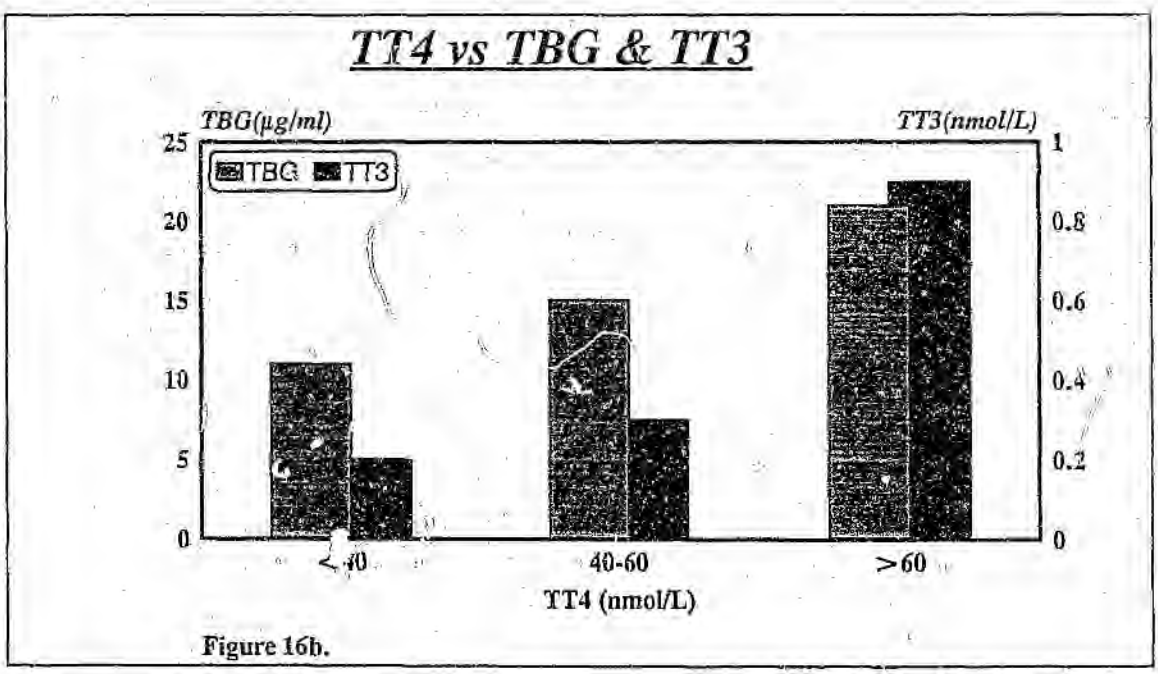


Figure 16b.

8.1.4 APACHE II.

APACHE scores are divided into mild severity ($\leq$ 12), moderate severity (13-25), and intense severity scores ($\geq$ 26).

APACHE Range	n	Mean
<13	18	7.6
13-25	26	17.8
>25	5	27.6

As the severity of illness increased (ie. APACHE II score increased), so did the mortality rate (Chi-Square = 14.6, p = 0.0007). The TT4, TT3 and TBG decreased as the APACHE II score increased (p = 0.03; 0.001; 0.02 respectively). No difference was found in TSH levels between the three groups. (figure 17).

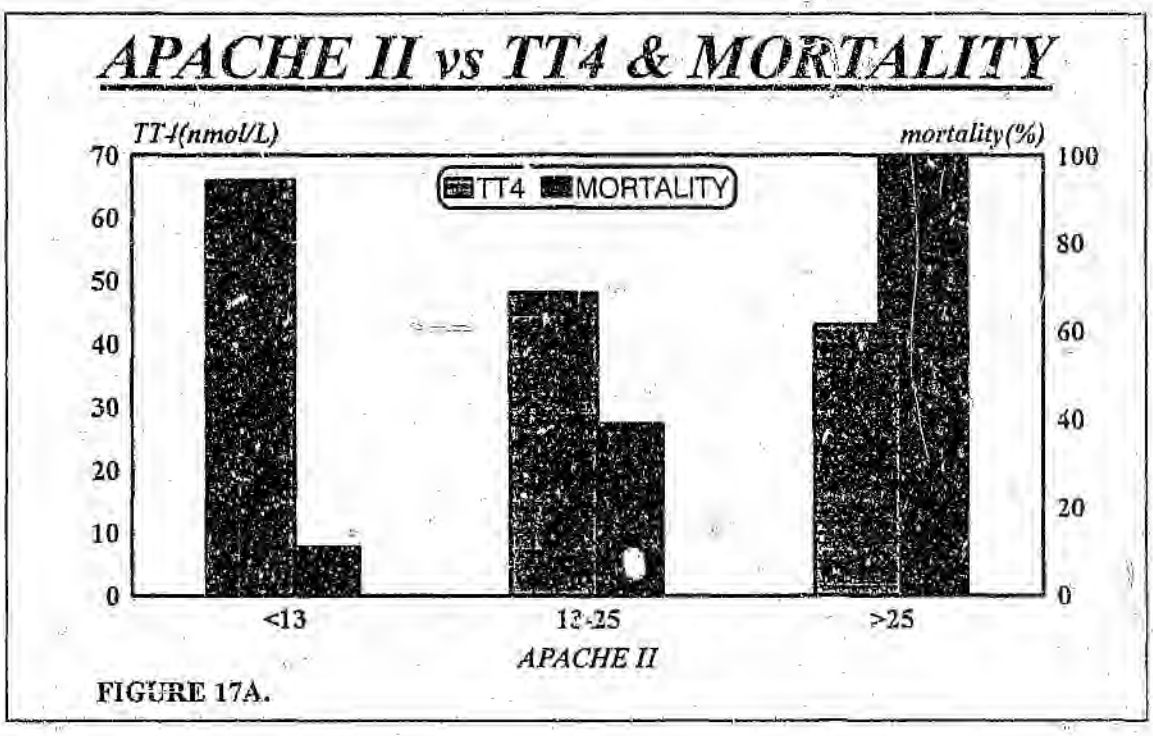


FIGURE 17A.

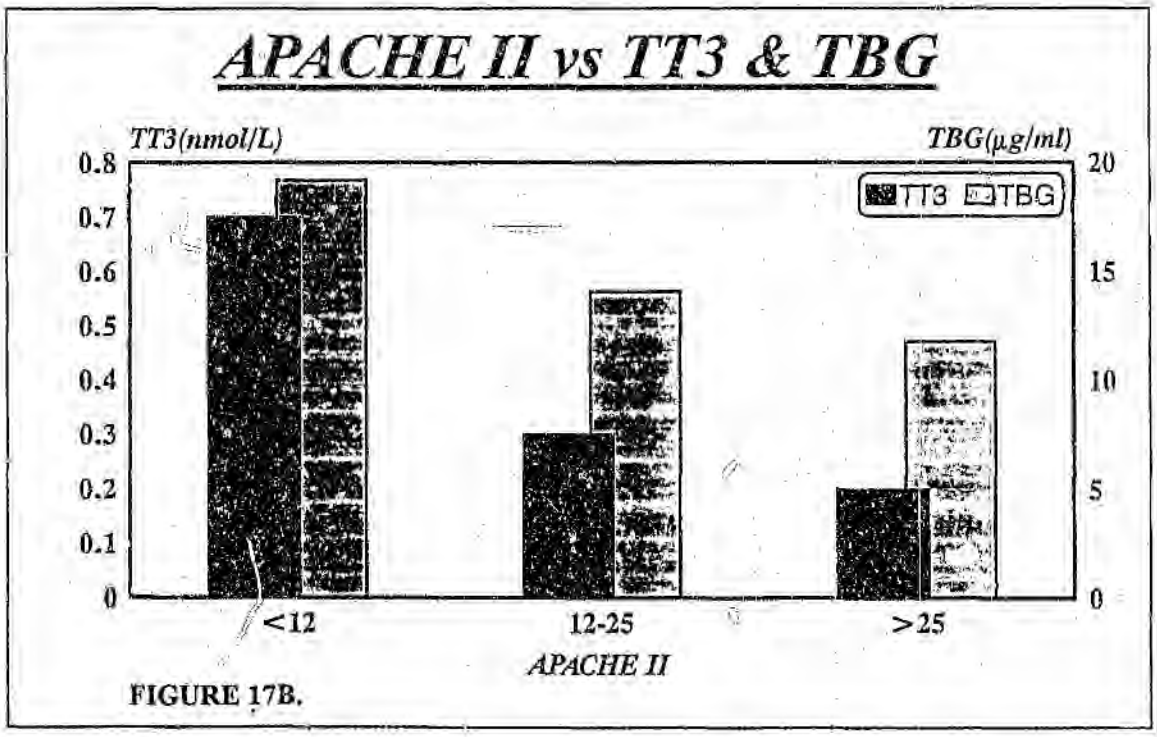


FIGURE 17B.

8.1.5 OUTCOME.

Admission data was analyzed according to whether the patient was a survivor (n = 32), or non survivor (n = 16) for their ICU stay (Figure 18).

Non-survivors had a significantly lower mean TT3 on admission (p = 0.02) and higher APACHE II score (p = 0,001) than survivors. Although the mean TT4 was lower in non-survivors, the difference between the two was barely significant (p = 0.06).

Age did not appear to affect outcome. The mortality rate in patients $\leq$ 60 years was 45% compared to 50% in patients greater than 60 years of age.

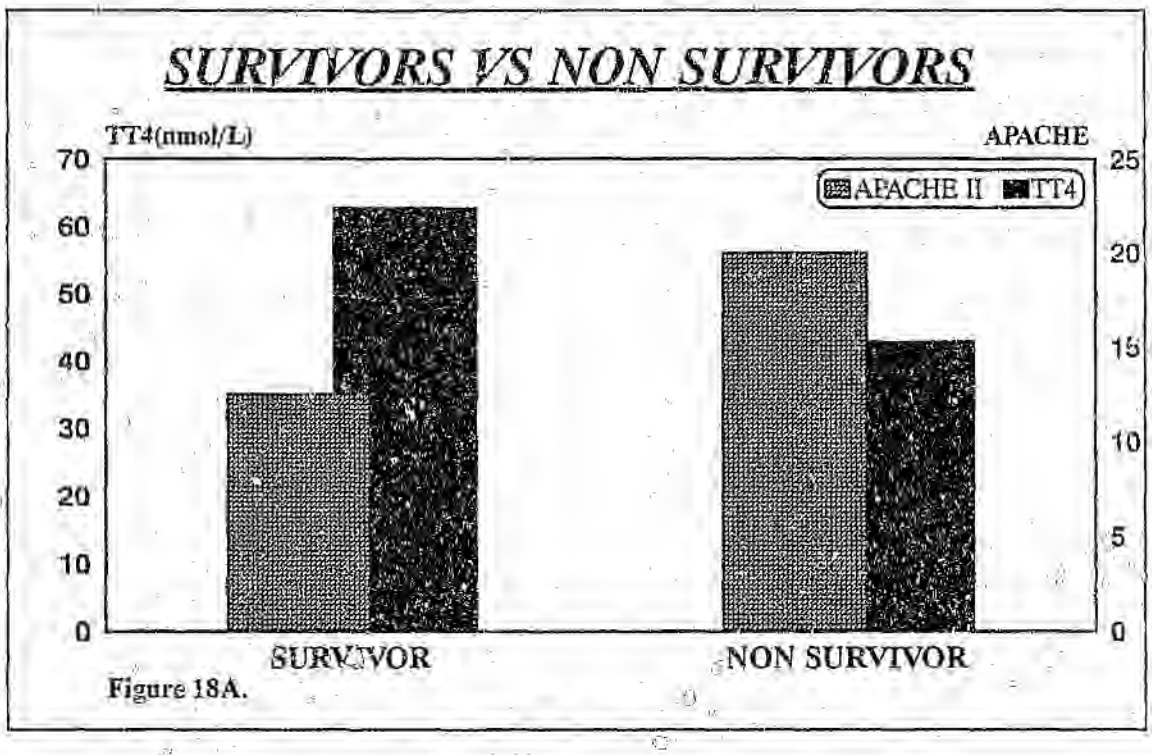


Figure 18A.

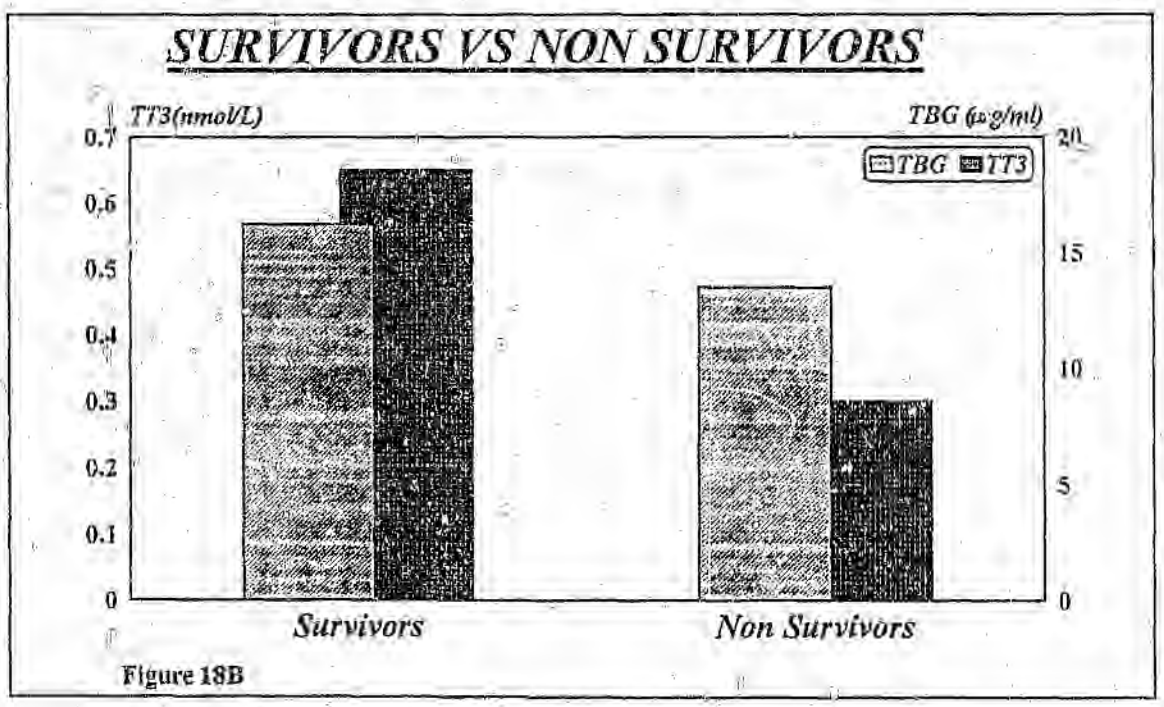


Figure 18B

8.2 TREND ANALYSIS.

Patients assigned to the septic syndrome group had serial serum thyroxine levels taken three times per week for up to three weeks. If the patient progressed from the septic syndrome group to the septic shock group full thyroid function tests were done at this time. Figure 19 (A&B) demonstrates the trend in serum thyroxine levels in survivors and non survivors.

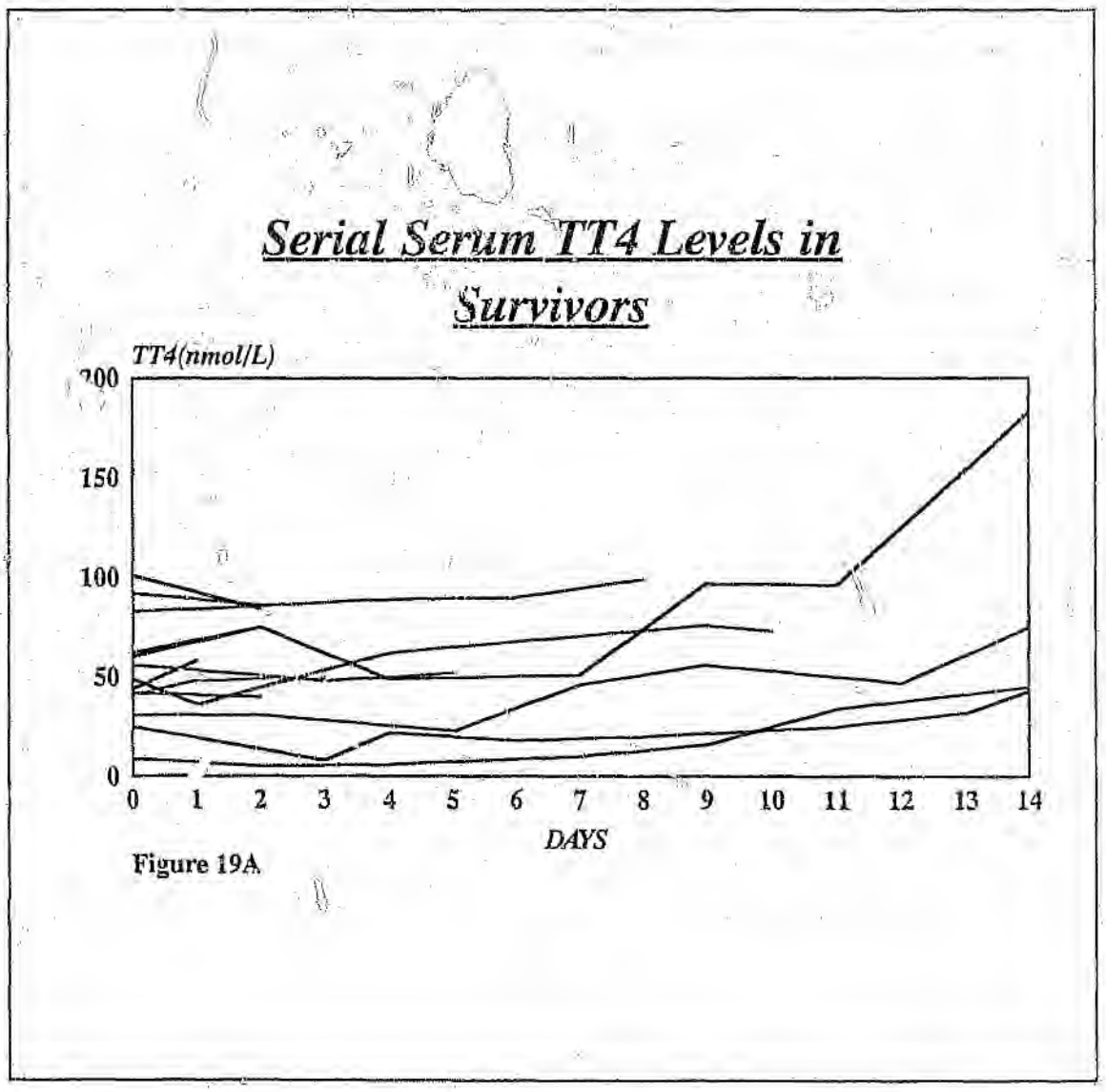


Figure 19A

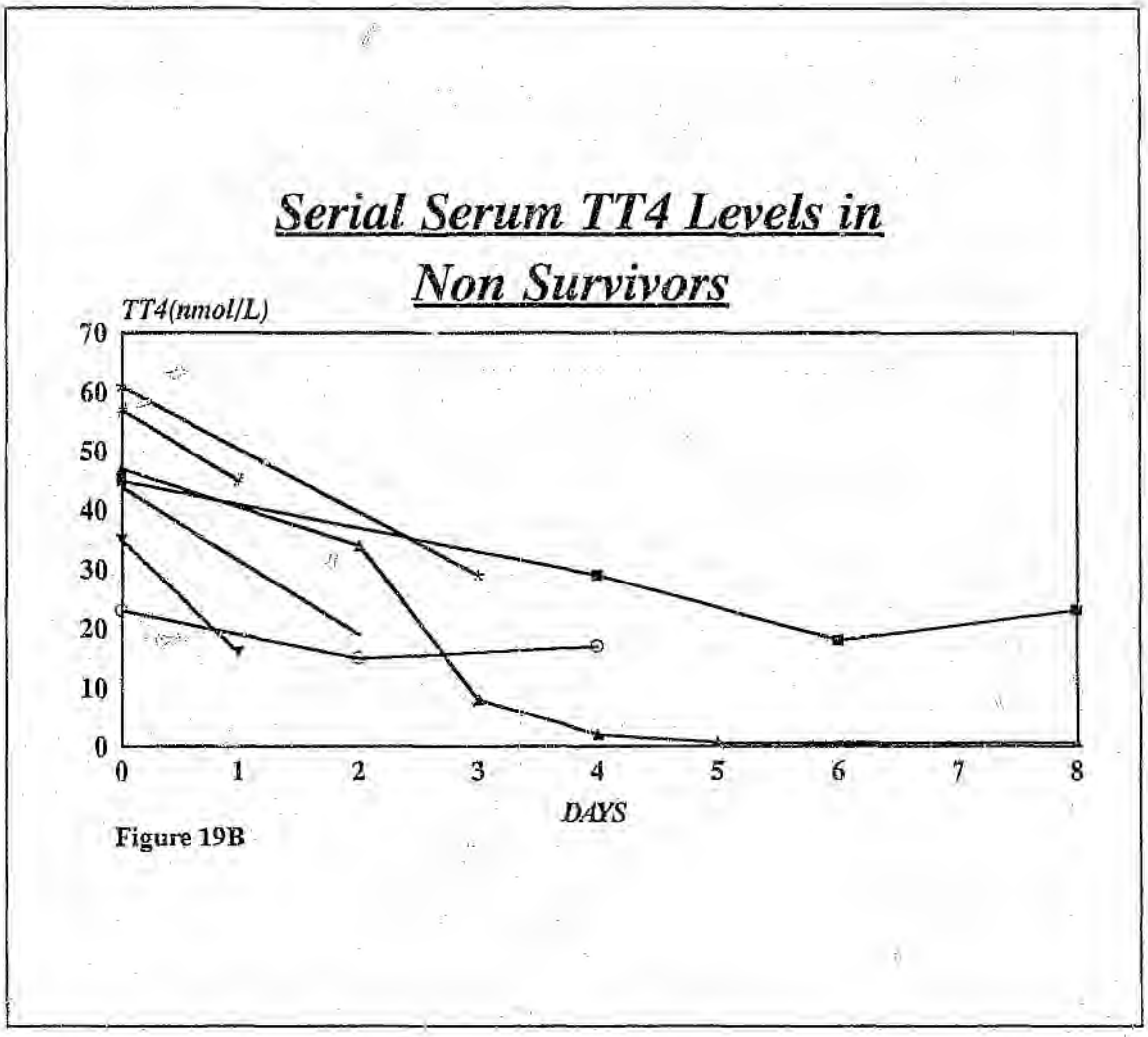


Figure 19B

8.2.1 Admission, Nadir and Discharge Serum Thyroxine Levels in Survivors and Non Survivors.

Twenty patients had APACHE II scores and serum TT4 levels on admission and just prior to discharge (or death) available for analysis (Figure 20).

The mean serum thyroxine level from admission to discharge or death, increased in survivors and decreased in non survivors.

The difference between survivors and non survivors for the change in mean TT4 was significantl ($p = 0.003$).

The nadir of the serum TT4 in survivors occurred at day 2.1 and day 3.6 for non survivors. In survivors the serum TT4 then increased to the discharge value (Admission TT4: 54.1nmol/L, lowest TT4: 47.4nmol/L, Discharge TT4: 73.9nmol/L). Non survivors failed to increase their nadir serum TT4 prior to death (admission TT4: 44.5nmol/L, lowest TT4: 19.4, TT4 just prior to death: 20.6nmol/L).

Survivors vs Non Survivors. Seurm TT4 on Admission, nadir and discharge.

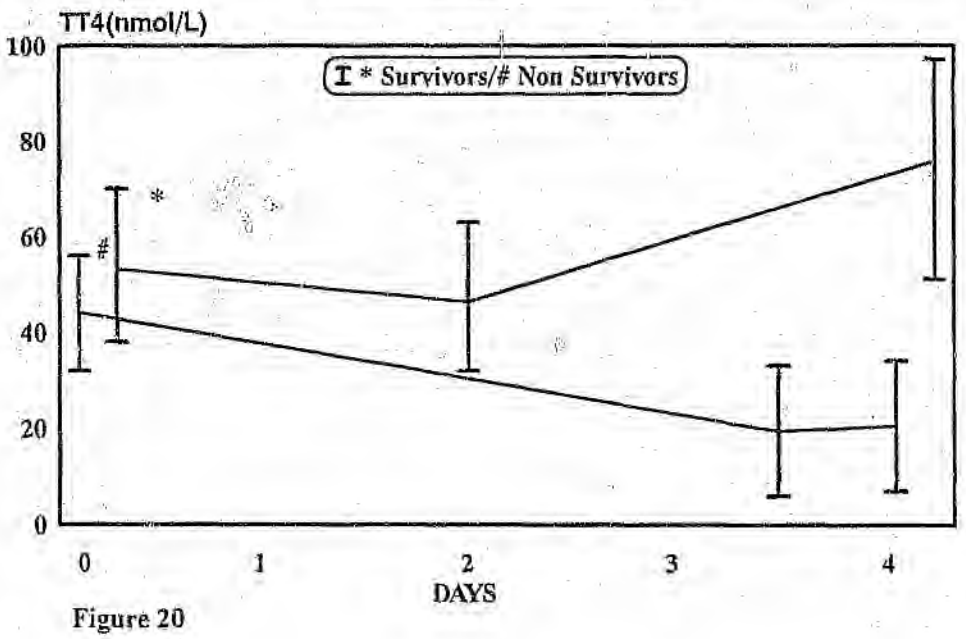


Figure 20

The predictive power of the nadir TT4 was analyzed by dividing the patients into two groups;

	Survivors	Non Survivors
i) Nadir TT4 < 35	3	6
ii) Nadir TT4 $\geq$ 35	10	1

A significant difference was found between the two groups (Chi-Square = 7.21, p <0.01). A serum thyroxine level less than 35nmol/L correctly predicted mortality in 66.7% of the patients, where as a serum thyroxine level greater than 35nmol/L correctly predicted survival in 90% of the patients.

8.2.2 Progression to Septic Shock.

Progression from septic syndrome to septic shock occurred in six patients at a mean of 1.8 days (Table 10). None of the changes that occurred in serum thyroid hormone levels was significant.

Table 10. Septic syndrome to septic shock.

	APACHE	TBG µg/ml	TSH µIU/ml	TT3 nmol/L	TT4 nmol/L
Δ S/SYN to S/S.	0	3.8	0.38	0.05	19.70
p value	N/S	N/S	N/S	N/S	N/S

9.0 Discussion.

9.1 Sepsis

As alluded to in the introduction, confusion still exists regarding the definitions of sepsis (204). Literature pertaining to the effects of sepsis on thyroid hormone economy similarly lacks clarity in the definition of sepsis. Although minor differences exist for specific infections, e.g., malaria, meningitis and pneumococcal infections, most infections associated with a sepsis response have characteristic changes in serum thyroid hormone levels (181), similar to those seen in other non thyroidal illnesses.

The definitions of sepsis in this study are based on internationally accepted recommendations (202). A clinical scoring system {APACHE II (229)} was used in an attempt to quantify the severity of illness. To my knowledge this is the first time that alterations in thyroid hormone levels in sepsis , using the described definitions, has been documented.

It is of interest to examine the composition of patients in each of the clinical sub groups, i.e., non-septic, septic syndrome and septic shock. The small number of patients in the septic shock group (n=8) is due to the relatively rare occurrence of septic shock on admission to ICU. Females accounted for 75% of patients in this group, half of whom had had a septic abortion. This illustrates the possible disastrous consequences of illegal abortions. Community acquired pneumonias accounted for the remaining diagnoses. The septic syndrome group had the largest number of patients (n=25), as it is not uncommon for most ICU admissions to be septic on admission. The male:female ratio was 66:44%. Community acquired pneumonias, abdominal and gynaecological sepsis accounted for most of these diagnoses. In the non septic group the male:female ratio was 47:53% and asthma, myocardial infarcts and post surgery were the commonest reason for admission.

There was no significant difference in the mean age between the three groups (N/S; 42, S/SYN;

34.6, S/S; 40.6). On the whole therefore, the patients in this study were relatively young, without preexisting disease.

The use of dopamine and heparin is common in intensive care units. Calciparin, the calcium salt of heparin, is used in almost all patients in the ICU who do not have contraindications to its use. In the septic syndrome group, no difference existed in the use of dopamine between non survivors and survivors. In the septic shock group dopamine was used in 6 of the 8 patients. Steroid use was uncommon, and was used predominantly in the treatment of asthma. Unfortunately it is difficult to identify the effect the use of these drugs may have had on thyroid hormone economy, in this study.

The alterations that occur in circulating thyroid hormone levels, with the onset and progression of the sepsis response, is well documented in both animal (184) and human studies (185). Dennhardt et al (185) followed changes in thyroid hormone levels in 15 patients who became septic postoperatively. With the onset of sepsis the rT3 and serum diiodotyrosine (DIT) levels increased significantly, while T3 and T4 levels fell below the normal range. DIT appears to be a relatively specific serum parameter for the presence and course of severe bacterial infection (186,185).

The present study confirms that changes in serum thyroid hormone levels do occur in sepsis, and the degree of alterations increase as the systemic response to infection increases. Alterations in thyroid hormones that occurred in the septic syndrome and septic shock groups were characterised by a low T3, low T4 and low TBG levels. Thyrotropin levels remained normal.

Patients in the septic syndrome group with a similar severity of illness to non septic patients (APACHE II < 20), had lower levels of thyroid hormones, although only TT3 was significantly different ($p = 0.001$). It could be argued however that this is an unfair comparison as the spectrum of primary diagnoses in the two groups is not the same. Although the APACHE scores are similar, there was a significant difference in mortality ($p = 0.02$), thus indicating that the septic syndrome group was probably sicker.

The observed changes that occur in circulating thyroid hormone levels in NTI, as a result of changes that may occur at different levels in the hypothalamic, pituitary, thyroid (HPT) axis (Figure 8), has previously been alluded to.

Cytokines are pivotal in the pathogenesis of the sepsis response, in particular TNF alpha and interleukin-1. Recent data indicate that TNF-α acts on the HPT axis at multiple levels (187,188,189), and that TNF-α may be one of the mediators responsible for alteration in thyroid function tests in sepsis. Interleukin-1 however has not been found to be contributory.

The alterations that occur in each of the thyroid hormones will be discussed separately in greater detail.

9.2 Serum Triiodothyronine.

A low TT3 is the commonest reported abnormality of thyroid function in non thyroidal disease (34,44,45). Seventy three percent of our patients admitted to ICU had a low TT3 level, in keeping with that reported by Bermudez et al (34).

The median TT3 in the non septic group, although normal is lower than that for the control group. As the severity of illness increased, i.e., the APACHE II score increased, or degree of sepsis increased (S/SYN vs S/S), so the median TT3 decreased ($p = 0.001$).

In critically ill patients TT3 decreases first followed by a decrease in TT4 (44,56). Our data confirms the presence of the low T3 and low T3, low T4 syndromes.

The cause of the decrease in serum T3 in NTI, is due to a decrease in peripheral production of T3 from T4. This occurs as a result of diminished activity of the 5'-deiodinase enzyme (35,41,51). The concomitant increase in rT3 is also due to reduced activity of the 5'-deiodinase enzyme. In critical illness inadequate nutrition and increased glucocorticoid secretion may contribute to the diminished activity of the 5'-deiodinase enzyme.

Although different pathogenetic mechanisms exist for the decrease in TT3 and TT4, in the low T3-low T4 syndrome, both occur simultaneously and proportionately. Thus it is not surprising

that a good correlation was found between TT3 and TT4 ($r = 0.84$, $p = 0.0001$). Custro et al (236) postulate that a low T3 level on admission in patients with NTI is indicative of a poor prognosis. In their study, patients with an initial T3 level less than 0.4nmol/L had a 84% mortality rate. In our study only 48% of patients with an admission T3 less than 0.4nmol/L died. However the median admission TT3 for survivors was 0.65nmol/L as opposed to 0.3nmol/L for non survivors ($P = 0.017$). Eisenberg et al (104) described similar results for their patients.

Since the serum T3 is significantly decreased in a large proportion of patients with NTI, measurement of T3 is of limited value in (i) the diagnosis of thyroid c sfunction and (ii) as a measure of outcome, in patients with significant NTI.

9.3 Serum Thyroxine .

Immediately following the onset of infection serum thyroxine falls (181). Both the decline in thyroidal release of thyroxine or it's accelerated disappearance due to increased cellular uptake, and the effect of inhibition of hormone binding to transport proteins, may account for the low level seen in infection (60,176). The initial decline of thyroxine, particularly in malaria, is followed by a rise to levels greater than for controls, during recovery (180,181).

Serum total thyroxine was measured on admission in all groups and serially in the septic syndrome group. The reason that TT4 was chosen to measure serially, is that TT4 has previously been documented to correlate with severity of illness and outcome (103,104,105).

The admission data will be discussed first followed by the relationship between serum thyroxine levels, clinical progress and outcome.

Oppenheimer et al (33), were among the first to report a subnormal serum T4 occurring in 50% of patients with NTI. Dennhardt et al (185) report that 37% of postoperative patients who became septic had a low T4 syndrome. Whereas Slag et al (105), found that only 22% of ICU

admissions had a reduced serum T4.

In our study 33% of patients in the non-septic group had a low T4, whereas 75% of patients in the septic syndrome and septic shock groups had a low serum T4 level. The difference in T4 levels between the groups was significant ($p = 0.05$).

Elaine M Kaptein (57) states that the type and magnitude of the alterations in serum T4 values do not appear to be unique for a specific disease state, but may reflect primarily the severity of illness or the associated catabolic state. Hadjikostova et al (184), using a septic shock rat model showed that as the degree of sepsis worsened, so did the decline in thyroid hormone levels.

When the severity of illness was assessed using the APACHE II score, the TT4 was lower in patients with a severe intensity of illness (APACHE II > 25) when compared to those with a mild severity of illness (APACHE II < 13) ($p = 0.03$). Similarly the lower the mean TT4 on admission, the higher the mean APACHE II score and mortality ($P = 0.02$ & 0.03 respectively). This data is in keeping with what is proposed by Kaptein, that is as the degree of sepsis worsens and the greater the severity of illness, the lower TT4 tends to be.

Free thyroxine by equilibrium dialysis (FT_4D), in patients with moderately severe illness is usually normal or increased (57). The clinical usefulness of measuring free thyroxine in NTI has been questioned. Slag et al (235) comment that as all methods of free thyroxine measurement in critically ill patients are non specific, free thyroxine assays should not be used to screen for thyroid disease in this group of patients. Aletta Smith in her dissertation on "Free thyroxine levels and altered thyroid hormone binding in nonthyroid illness" (237) concludes that, as the controversy around the bioavailability of thyroxine during NTI is unsolved, it remains uncertain whether the measurement of free thyroxine in NTI is appropriate. Muller and Hesch (238) state that iodothyronine metabolism is strongly organ specific, and that alterations in plasma thyroid hormone levels cannot reflect cellular or subcellular thyroid hormone concentrations in individual organs.

Free thyroxine levels were not measured in this study due to financial constraints. This may have been desirable however, as free thyroxine is measured as part of the thyroid function

tests, done at Baragwanath hospital.

The T4:TBG ratio is a reflection of free thyroxine. Slag et al (235) demonstrate an excellent correlation between the T4:TBG ratio and the FT_4I ($r = 0.91$, $p < .01$), and a good correlation with free T4 (equilibrium dialysis) ($r = 0.61$, $P < 0.01$). Melmed et al (39) report subnormal FTI levels in 71% of intensive care patients. Chopra et al (37,40) document a significant increase in dialysable free thyroxine in NTI. This is postulated to occur as a result of a circulating inhibitor. In our study a downward but insignificant trend for the TT4:TBG ratio was found in the N/S, S/SYN and S/S groups. This would suggest that the decrease in TBG was not a major determinant of the low TT4 level. The insignificant change in the T4:TBG ratio would support the presence of an inhibitor.

The relationship between serum thyroxine levels and the clinical progress and outcome is well described. The serum thyroxine level on admission has been shown to be predictive of outcome. Eisenberg et al (104) report that 55% of non survivors had an admission TT4 of less than 4.5μg/dl (58nmol/L). Slag et al (105) found that patients who had a serum thyroxine level of less than 3μg/dl (38.6nmol/L) on admission had an 84% mortality rate. In our study the admission TT4 was lower in non survivors than survivors (45nmol/L vs 54nmol/L), and an admission TT4 < 40nmol/L was associated with a 53% mortality compared to a mortality of 11% if the TT4 was normal i.e. > 60nmol/L ($p = 0.03$).

McLarty et al (99) demonstrated a progressive decline in T4 levels in patients who died as a result of a myocardial infarct or cerebrovascular accident. Kaptein et al (46) found that the mean nadir TT4 in 195 ICU patients, correctly classified outcome in 70% of patients overall, and that a nadir TT4 < 3μg/dl (38.6nmol/L) was associated with a 67% mortality.

In the present study non survivors were characterised by a progressive fall in TT4 until death. Survivors however demonstrated an initial (insignificant) drop in TT4 followed by a progressive increase to levels above the admission values. The difference in mean TT4 on discharge or just prior to death was significant ($p = 0.003$). The mean nadir TT4 in survivors was 47.4nmol/L and 29nmol/L in non survivors. A nadir TT4 of < 35nmol/L correctly predicted death in 66.7%

of patients, whereas a nadir TT4 $\geq$ 35nmol/L correctly predicted survival in 90% of patients. Therefore the nadir TT4 has an overall classification of outcome accuracy of 85%. The risk of a patient dying if the nadir TT4 was < 35nmol/L was 20 times greater than if the nadir TT4 was > 35nmol/L (Odds ratio = 20). The predictive accuracy of a nadir TT4 of less than 35nmol/L was chosen, as a value of less than this reflects severe hypothyroidism. Our data is therefore in keeping with published results.

In patients who progressed from septic syndrome to septic shock, the mean TT4 decreased insignificantly. This insignificant difference is probably the result of the continuum of sepsis that exists, and that the T4 level is unlikely to be significantly lower when the patient has just progressed to septic shock.

9.4 Thyroid Binding Proteins.

Thyroid binding prealbumin (TBPA) was not measured in this study. Albumin was measured as part of the routine work up on admission in some patients.

Earlier studies have shown little change in TBG levels with infective illnesses and that a correlation between free T4 and TBPA exists. These finding however have not been confirmed (181).

Thyroid binding globulin was mild to moderately reduced in our study population. In our study a good correlation between albumin and TBG was demonstrated ($r = 0.62$, $r = 0.0001$). Albumin is a low affinity, high capacity binder of thyroxine, and tissue availability may be decreased as a result of the reduced albumin bound fraction (75).

9.5 Thyrotropin.

In NTI basal TSH levels are generally reported as being normal (45,39), and this observation led to the speculation of altered hypothalamic-pituitary responsiveness. However TSH can be

depressed in some critically ill patients, and during recovery from NTI may rebound to supranormal levels (118,39,116). Earlier studies reveal an initial suppression of TSH release followed by a compensatory phase of accelerated secretion (181). Schutte et al (239) found normal TSH levels, using both conventional and ultrasensitive assays, in non critically ill patients with febrile illness. The ultrasensitive assay was also found to be a reliable screen of thyroid disease in NTI, in comparison to FTI and the newer commercial assays for FT4. **It is well documented that dopamine infusion will lower basal TSH and the TSH response to TRH (76).** Recently Rothwell et al (240), studied thyrotropin concentrations, using a sensitive TSH assay, in 200 consecutive patients on admission to ICU who were not receiving dopamine. Thyrotropin concentration was subnormal in 12% of patients and increased in 13% of patients. Admission thyrotropin concentrations were found to be of prognostic significance in these critically ill patients. Due to the high frequency of abnormal thyrotropin concentrations in this study, the authors question the assumption of euthyroidism in critical illness.

In this study thyrotropin levels were in the normal range in all three groups studied (i.e., N/S, S/SYN, S/S), and showed no correlation with any of the other thyroid hormones. One patient however had an elevated TSH level, providing biochemical evidence of hypothyroidism, and was therefore excluded from the study. There was no difference in thyrotropin concentration between survivors and non-survivors.

Our results are in contrast with those found by Rothwell et al, but may be accounted for by the small study size and dopamine administration in a significant number of our patients.

9.6 APACHE II Score.

The association between the APACHE II score, serum TT4 and fatal outcome has previously been documented. Boles et al (49) in patients with mild (APACHE $\leq$ 12), moderate (APACHE 13-23) and intense severity scores (APACHE $\geq$ 24), documented TT4 levels of 6.6ug/dl (84.9nmol/L), 5.4ug/dl (69.5nmol/L) and 4.3ug/dl (55.3nmol/L) respectively. The association between the APACHE II score and serum TT4 is not unexpected. The APACHE II score uses

acute physiological measurements in order to quantify the severity of illness, and as discussed previously the serum TT4 decreases as the severity of illness increases.

Our data confirms the association between TT4 and the APACHE II score. The difference in mean TT4 in each APACHE group on admission was significantly different ($p = 0.032$). The APACHE II score also correlated with TT3 ($r = -0.52$, $p = 0.0001$). As the APACHE II score increased (i.e., the severity of illness increased), so did the mortality rate (Chi-square = 14.6, $p = 0.0007$).

These results document the relationship between increasing quantified severity of illness and changes in thyroid hormone levels.

9.7 Conclusion.

Following the onset of almost any infection, serum T4 and T3 levels decrease as a result of decreased secretion of TSH and T4, accelerated T4 disappearance, inhibition of hormone binding to transport proteins and decreased peripheral T4 to T3 conversion.

The alterations in thyroid hormone economy described in this study are in keeping with those published for most infections.

Although previously stated that alterations in thyroid hormone levels are related to the severity of clinical infection (179), this has not been hither to quantified. In an attempt to quantify the severity of the sepsis response, recognised definitions of the body's systemic inflammatory response to infection (i.e., Septic syndrome;septic shock) have been used. This study confirms (i) significant differences in serum thyroid hormone indices at presentation in critically ill, non septic and septic patients; and that (ii) the development of sepsis worsens the severity of alterations in serum thyroid hormone indices and mortality.

The prognostic significance of TT4 in critically ill patients and its relationship to the APACHE II score is documented in the literature (46,105). The APACHE II scoring system has been validated as a useful prognostic tool for patients with sepsis (230). The APACHE II score was used in this study in an attempt to quantitate the severity of illness, and compare with serum

thyroxine levels for outcome. Serum thyroxine was predictive of outcome as evidenced by (i) an admission TT4 of less than 40nmol/L was associated with a 53% mortality and (ii) a nadir TT4 was associated with an overall predictive accuracy of outcome of 85%.

Survivors and non survivors have characteristic changes in their serial TT4 levels. Non survivors demonstrate a progressive decline in TT4, while in survivors a rebound phenomenon occurs with TT4 reaching values higher than the admission level.

The admission APACHE II score was a better predicter of mortality than the admission TT4 (Chi-square = 14.6, p = 0.0007 and Chi-square = 7.0, p = 0.03 respectively).

Although the nadir TT4 had the greatest predictive accuracy, this would be difficult to use in clinical practice due to the serial TT4 levels required to determine the nadir. In my opinion therefore serum thyroxine should not be used as a "bedside" prognosticator of outcome.

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APPENDIX: RAW DATA

Appendix 1:

Admission Data: Non-septic patients.

Study No.	Date	APACHE II	TBG	TSH	TT3	TT4	Out Come	ALB
A01	1/4/91	9	20.0	0.7	0.7	76.4	A	25
A02	8/4/91	18	16.6	1.5	0.9	72.0	A	
A03	12/4/91	11	22.9	0.8	1.0	80.4	A	
A04	3/5/91	6	8.5	0.9	0.4	44.8	A	
A05	16/5/91	16	16.7	2.7	0.9	66.2	A	35
A06	27/5/91	5	14.6	2.3	1.4	75	A	
A07	28/5/91	11	23.9	3.7	1.6	97.2	A	
A08	30/5/91	18	14.9	3.5	0.2	30.4	A	28
A10	8/6/91	25	17.5	1.4	0.3	29.6	A	31
A11	14/6/91	10	20.9	2.9	1.3	89.4	A	
A12	23/6/91	12	35.7	1.8	0.7	66.2	A	
A13	28/6/91	17	16.2	2.8	1.2	70.1	A	36
A14	3/7/91	10	16.1	2.4	0.9	59.3	A	31
A15	19/7/91	1	14.7	1.1	1.4	80.5	A	40
A16	5/7/91	3	18.2	2.1	0.7	40.2	A	34

Outcome: A = Alive, D = Dead.

Admission Data: Septic syndrome patients.

Study No.	Date	APACHE .II	TBG	TSH	TT3	TT4	Out Come	ALB
B01	19/3/91	14	11.4	1.4	0.5	56.6	D	37
B02	3/4/91	13	8.2	2.5	0.1	30.5	A	22
B03	4/4/91	17	20.9	1.0	0.6	83.4	A	
B04	4/4/91	14	23.7	0.9	1.0	101.3	A	41
B05	7/4/91	10	9.6	2.8	0.3	40.6	A	19
B06	10/4/91	14	10.3	1.3	0.3	43.7	D	21
B07	29/4/91	15	18.9	1.5	0.7	71.0	A	35
B08	6/5/91	15	10.3	0.8	0.1	8.8	A	21
B09	9/5/91	16	9.7	1.0	0.1	24.7	A	31
B10	14/5/91	19	8.2	2.4	0.3	42.0	D	
B11	31/5/91	8	15.5	1.9	0.2	55.7	A	
B12	2/6/91	10	17.6	1.9	0.4	44.3	A	
B13	9/6/91	21	12.4	1.1	0.2	48.5	A	22
B14	11/6/91	4	23.5	1.4	1.0	91.5	A	32
B15	16/6/91	20	6.2	5.6	0.2	47.4	D	33
B16	20/6/91	17	16.3	1.4	0.2	55.1	D	42
B17	21/6/91	19	13.1	0.7	0.3	65.5	A	27
B18	24/6/91	4	14.1	0.7	0.3	59.9	A	
B19	24/6/91	20	7.5	1.8	0.1	22.7	D	18
B20	26/6/91	18	15.5	1.1	0.2	41.9	A	27
B21	4/7/91	28	12.8	2.0	0.2	35.4	D	27
B22	26/7/91	23	16.3	2.6	0.3	34.7	D	26
B23	27/7/91	12	26.8	0.9	0.6	45.2	D	37
B24	23/8/91	14	19.5	0.8	0.3	60.5	D	27
B25	27/8/91	7	27.9	3.3	1.4	98.0	A	35

Admision Data: Septic shock group.

Study No.	Date	APACH E.II	TBG	TSH	TT3	TT4	Out Come	ALB
C02	16/4/91	20	20.8	1.2	0.4	66.1	D	31
C03	3/5/91	22	10.3	3.6	0.4	32.4	A	30
C04	10/6/91	26	9.1	0.6	0.2	32.4	D	23
C05	17/6/91	30	22.7	0.7	0.8	97.4	D	
C06	4/7/91	27	7.1	5.1	0.2	39.8	D	
C07	4/7/91	27	7.1	1.5	0.1	9.4	D	
C08	1/8/91	17	7.2	1.5	0.2	24.9	A	20
C09	26/8/91	9	14.2	3.4	0.4	39.1	D	

Appendix 2: Serial TT4 Levels in Septic Syndrome Group,
& Repeat TFT's in patients who progressed to Septic Shock.

Study No.	Day	TBG	TSH	TT3	TT4
B01	0	11.4	1.[illegible]	0.5	57
	1				45
B02	0	8.2	2.5	0.1	31
	2				31
	5				23
	7				46
	9				48
	12				56
	14				47
	16				75

Appendix 2: (continued)

Study No.	Day	TBG	TSH	TT3	TT4
B03	0	20.9	1.0	0.6	83
	1	18.7	0.7	0.6	84
	4				89
	6				90
	8				99
B04	0	23.7	0.9	1.0	101
	2				84
B05	0	9.6	2.8	0.3	41
	1				48
	3				50
B06	0	10.3	1.3	0.3	44
	2				19
B07	0	18.9	1.5	0.7	71
	1	18.9	0.7	0.6	62
	2				75
	4				49
	7				51
	9				97
	11				96
	14				183

Appendix 2 (continued)

Study No.	Day	TBG	TSH	TT3	TT4
B08	0	10.3	0.8	0.1	9
	2				5
	4				6
	7				105
	9				16
	11				34
	14				32
	15				45
B09	0	9.7	1.0	0.1	25
	3	8.7	6.4	0.1	8
	4				22
	6				18
	8				20
	11				25
	13				32
	16				40
	18				43
B10	0	8.2	2.4	0.3	42
	1				54
	3				57
	6				49
	8				63
	11				65
	13				52
	15				39
B11	0	15.5	1.9	0.2	56
	3				48
	5				52

Appendix 2 (continued).

Study No.	Day	TBG	TSH	TT3	TT4
B12	0	17.6	1.9	0.4	44
	1				58
B13	0	12.4	1.1	0.2	49
	1				36
	4				62
	5				65
	9				76
	10				73
B14	0	23.5	1.4	1.0	92
	2				86
B15	0	16.2	5.6	0.2	47
	2				34
	3				8
	4				1.5
	5				0.7
	8				0.7
B16	0	16.3	1.4	0.2	55
	1	11.1	1.0	0.2	28
	2				10
	3				12
	4				9
B17	0	13.1	0.7	0.3	66
	3				39
B18	0	14.1	0.7	0.3	60
	2				75
B19	0	7.5	1.8	0.1	23
	2				17
	4				9

Appendix 2 (continued)

Study No.	Day	TBG	TSH	TT3	TT4
B20	0	15.5	1.1	0.2	42
	2				40
B21	0	12.8	2.0	0.2	35
	1	8.2	0.8	0.1	16
B22	0	16.3	2.6	0.3	35
B23	0	26.8	0.9	0.6	45
	4				29
	6				18
	11				26
B24	0	19.5	0.8	0.3	61
	3				29
B25	0	27.9	3.3	1.4	98
	1				71

Appendix 3: Controlls.

	TBG	TSH	TT3	TT4
Males	18.7	.3	1.2	70.8
	6.1	1.4	1.3	117.5
	22.7	1.9	1.8	75.6
	19.3	2.7	1.6	77.9
	13.7	2	1.2	73.6
	16.7	2.7	1.4	74.6
	10.3	1.2	1.1	91.4
	17.8	1.2	1.4	111
	23	1.6	1.6	59.5
	8.9	3.1	0.8	79.5
	21.4	0.8	1.5	68.3
Females	19.2	1	1.3	77.1
	15.2	1.6	1.2	64.8
	31.1	2.1	1.2	81
	21	1.7	1.3	70
	21.6	2.2	1.3	65.8
	20.9	1.8	1.2	71.4
	17.4	1.9	1.3	52.7
	17.8	1.8	1.4	70.2
	31.6	1.5	1.9	99.5
	17.3	1.7	1	35.5
	26.6	3.2	1.9	88
	21.2	1.7	1.1	84

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