# PSYCHOMETRIC AND PSYCHOPHYSIOLOGICAL STUDY OF HYPERTHYROIDISM

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# HYPERTHYROIDISM

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SUMMARY

Chapter I: The aims of this study are outlined and the techniques intended for use are identified. Although the general pattern of feelings and mood states associated with hyperthyroidism were to be examined, anxiety was chosen as the mood state for specific study. The reasons for this decision are given. Attempt is made to clarify the meanings - and the inter-relationships of the words 'moods', 'emotion', and 'arousal'. The nature of anxiety is discussed; and the approaches to the study of the relationships between emotions and endocrine functions - i.e. psychoendocrinological research - are outlined. There was poor progress in this field of research until two decades ago. The reasons for this are discussed.

Chapter II: (a) The association between hyperthyroidism and emotional disturbance has been recognised since the early descriptions of the disease. Many physicians regard the psychological components of the disease as a form of neurosis, and there is a considerable body of opinion regarding it as the consequence of prolonged emotional stress. The term 'hyperthyroidism' encompasses a number of different conditions in which the thyroid is over-active. There is no evidence that the pattern of reported psychological disturbances differ between the different types of hyperthyroidism. The clinical features of hyperthyroidism are difficult to distinguish from those of anxiety neurosis. Definitive diagnosis is made on the bais of the laboratory tests of thyroid function. The aetiology is unkown, but there is evidence to suggest that thyrotoxicosis - one of the hyperthyroid states - is an auto-immune disease.

(b) Feelings are states of the self, and they defy all attempts to measure them directly. Only their indicants may be measured. The measurement - in this way - of patterns of feelings in general, and of anxiety in particular are divisible into two: (i) psychometric and (ii) physiological. Both these two approaches in measurement are described, and their validity and reliability discussed. The neuro-physiological basis of skin conductance measures is also described.

Chapter III: Sampling of the patients studies, and the experimental methods used outlined in this chapter.

Chapter IV: Results of the experiments and the psychometric tests are given. Comparison is made with data published for normal (healthy) populations - where these were available - and also with data published for diagnostic groups (anxiety neurosis, phobic states) considered to be of relevance.

Chapter V: The significances of the results obtained are discussed in terms of the knowledge available on the nature of the measurements used. From the results of the skin conductance measures, it could be concluded that the psychophysiological abnormality attributable to hyperthyroidism was hyperarousal, increased reactivity or responsivity, and hypersensitivity. These abnormalities improved when the underlying endocrine disorder was treated. It is argued that the physiological mechanism involved in the production of this abnormality is central autonomic rather than peripheral. With respect to the cardio-vascular measures, interpretation was more difficult. The reasons for this are discussed, and it is concluded that in spite of these, the involvement of the cardiovascular measures in the

emotional /

emotional aspects of hyperthyroidism could not be totally excluded. The results of the psychometric tests indicated the presence of a moderately severe degree of psychiatric morbidity and high level of anxiety in hyperthyroidism. The pattern of feelings in the hyperthyroid group was not different from that in the comparison group; and there was a tendency for the abnormality to improve as the underlying endocrine dysfunction was treated. The significance of this finding is discussed.

Chapter VI: Conclusions.

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"Of all the animals on the earth, man alone possesses a thyroid gland not only larger than the adrenal gland, but two or three times larger ..... the ratio of the combined weights of the brain, the thyroid, and the adrenal glands to the body weight is higher in man than in any other animals..... We now clearly see why man with his preponderating intelligence, preponderating brain, and preponderating thyroid gland so completely dominates the earth. Man alone works all day and worries all night. Man alone acquires exophthalmic goiter".

Dr. George CRILE

("The mechanism of exophthalmic goiter" - paper read at the 1938 Washington Conference of the American Goiter Ass.)

C O N T E N T S

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The Tables and Figures are placed on the pages following first reference to them.

# CHAPTER I

# I N T R O D U C T I O N

## 1. Aims of Study

The aims of this study were :

(a) To make a phenomenological study of the mood states associated with hyperthyroidism, using objective psycho-physiological indices and psychometric measures; and to compare the findings with those published for normal (healthy) populations.

(b) To observe any changes in mood during the treatment of the hyperthyroid state.

(c) To compare hyperthyroid patients with a group of euthyroid patients with symptoms similar to those of hyperthyroidism, but symptoms which were attributable to functional rather than organic illness.

It was proposed to observe the general mood pattern, and the degree of associated psychiatric morbidity. The decision to study anxiety specifically was made for three main reasons. Firstly, although various mood states have been reported in association with hyperthyroidism, anxiety seemed to be the most prominent and consistently reported. Anxiety neurosis is the main differential diagnosis for hyperthyroidism, both being difficult to distinguish from each other on clinical grounds alone (Strong 1968). Secondly, even when it was not present as the dominant mood state, it was likely to accompany any other mood state which might be predominating. Thirdly, psychophysiological techniques have been widely used in the investigation of anxiety; and the relationship between anxiety and the indices which the techniques measure are partially, though not fully, understood.

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## 2. Mood, Emotion and Arousal

There is a considerable variation in the meanings attached to these three words by different people. Perhaps the most acceptable definition of mood is that by Jaspers (1963): "Moods are states of feelings or frames of mind that come about with prolonged emotion which, while it lasts, colours the whole psychic life". This definition also illustrates the close relationship between mood and emotion. Hebb (1966) thought that mood was an emotional state, and he defined the latter as "The special state of arousal accompanied by mediating processes which tend to excite behaviour maintaining or modifying the present state of affairs". This definition was based on behavioural and neuro-psychological concepts, and it would appear to be no different from regarding emotions as feeling states that are aroused by, or accompany, various innate stimulus patterns or environmental changes. The usefulness of Hebb's definition is the attention focussed on the relevance of arousal to emotions, and therefore to moods.

The word 'arousal' is used by psychophysiologists to describe a variable along a continuum ranging from coma at one end through normal sleep, somnolence, wakefulness, to a state of vigil and psychomotor excitation at the other end. Its concept developed from the formulations of Duffy (1951), Lindsley (1951), and Hebb (1955). The glossary of terms in Hebb's Textbook of Psychology (1965) defined arousal as "wakefulness, alertness, vigilance, excitation, or excitability; at high levels, emotional disturbance". He regarded arousal as the product of sensory excitations of cortical activity through non-specific afferent pathways.

According /

According to Epstein (1967), arousal is a more fundamental feeling state than emotion. It is built into the organism and can be detected in infants long before specific emotions can be. Stimulus intensity is the most important factor in its production. When arousal is too intense for the individual's normal adaptive capacities, emotional disturbance may then ensue.

The mechanism by which emotional disturbance occurs in high arousal states is unknown. It is possible that both are reflecting different levels of the same neuro-psychological process. It is well known and established that provoked emotional states or mental stress can produce changes in the peripheral physiological indices of arousal, such as fore-arm blood flow, sweat activity, and heart rate. The James-Lange theory of emotion, on the other hand, regards emotional states as the consequence of the peripheral autonomic manifestations of arousal. This theory fails to account for the absence of a concommitant emotional disturbance in some patients with states of high physiological activity - phaeochromocytoma, hyperthyroidism. It appears, however, to have been supported by some recent studies (Frohlich et al 1966).

## 3. The Nature of Anxiety

According to Sheldon Korchin, quoted by Pichot (1969), anxiety may be referred to as any of the following :

(a) an unconscious determinant of behaviour;

(b) a major symptom of psychopathology;

(c) a uniquely human phenomenological experience;

(d) /

(d) a discharge of the autonomic nervous system;

(e) an essential condition for socialisation of the child;

(f) a drive of central importance in the behaviouristic study of human and animal learning.

Anxiety may also be a state or a trait. Although anxiety is common as a response to changing circumstances, it is evident that the levels of response in some people vary about a given point which is typical for them. This phenomenon, which is a trait, has been described as 'characterological anxiety' by Cattell (1965).

In psychiatry, anxiety is usually equated to the state of emotional response in which there is apprehension, tension and worry. In a factor analytic study of mood states, done by means of adjectives check lists, Lorr et al (1967) found that one of the factors which emerged was a Tense-Anxious factor. This factor consisted of seven adjectives listed below with the correlations they had with the Tense-Anxious factor :

| | |
|---|---|
| Nervous | 0.59 |
| Anxious | 0.53 |
| Shaky | 0.39 |
| Worried | 0.36 |
| Jittery | 0.36 |
| Tense | 0.31 |
| On Edge | 0.30 |

Fear and anxiety are identical emotional states. Many psychiatrists believe that the distinction between the two is artificial.

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They therefore refer to the former as "situational anxiety state". Jaspers (1963), however, considered the two as separate. He pointed out that whereas fear was directed towards something, anxiety was free-floating and unattached. Anxiety, according to him, was generally a primary psychic state, usually linked with a strong feeling of restlessness - an emotional state of inward excitement.

4. Emotion and Endocrine Function

The study of the emotions in relation to endocrine functions belongs to the field of psychoendocrinology. The term was coined by Reiss, in 1955, apparently in an attempt to revive interest in this branch of medicine. He wished to re-orientate research on a more organised and proper scientific footing, away from the previous erratic and confused approach to the subject. Interest in psycho-endocrine relationships has existed since the time of Kraepelin, one of the founders of clinical psychiatry, who expected endocrinology to provide the final solution to the pathogenesis and treatment of some psychiatric disorders. Kraepelin (1890) taught that every psychiatric disorder, especially the psychoses, had a specific underlying metabolic or endocrinological abnormality. It was this conviction which led him to believe that the converse must be true also with regard to physical illness associated with mental disturbances.

There are two main approaches to the study of psychoendocrine relationships.

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(a) Study of Endocrine Functions in Psychiatric Patients. This method has been used by such workers as Hoskin and Sleeper (1930), Reiss (1954), Gjessing (1938), and more recently by Lorraine (1970). A variation of this approach is to induce some psychological state (fear, anxiety or anger) in a subject and see if there are any associated changes in the endocrine function of the individual. This method was used by Franz Alexander and his colleagues (1961), employing the film, "Wages of Fear" as an anxiety-provoking stimulus.

(b) Study of Psychopathology in Patients with an Endocrine Disease. Studies adopting this approach appear to be more commonly reported in the literature than those adopting the first approach. This is especially so with regard to thyroid gland dysfunctions. Examples among these are studies by Conrad (1934), Moschcowitz (1930), Lidz (1949), and Ham, Alexander and Carmichael (1951). This approach was adopted for the present study.

Psychoendocrine research is bedevilled by multitudinal factors which need to be taken into account by the research worker who hopes to derive meaningful and useful information from the results of his experiments. Reiss (1967) has reviewed progress in this field, and analysed the factors which seemed to have been responsible for the poverty of sensible results and progress. These factors are summarised below :-

(i) There was a great deal of misconceptions by earlier workers about the role of the endocrine glands. It was believed, for example, that deductions made from animal experiments could be transferred uncritically to human subjects.

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Thus when it was observed that the total sex activity in animals could be changed by application of sex hormones, there was a wide-spread belief (and trials too) that human male homosexuals might be treatable with testosterone. Similarly, there was a wide-spread attempt to treat schizophrenia with thyroid extract after the publication by Hoskin and Sleeper (op. cit.) of the successful treatment of a few patients with this disease. There was no attempt to assess the endocrine status of the patients prior to treatment. The wide-spread failure, which would be expected in the circumstances, led to thyroid treatment being discredited generally.

(ii) Researchers have tended to use cross-sectional investigations only, investigating one single biochemical factor, and using small samples of hospital patients. There was no evidence that these samples were selected at random, and hence make the results apply to large groups; or that they were a homogeneous group. In addition controls were not often studied identically. In this way results from different research groups were often incomparable. The publication by Gjessing (op. cit.) seemed to have failed to imprint the importance of longitudinal investigations in yielding much more valuable information.

(iii) Psychiatrists who have ventured into the field of psycho-endocrinology have tended to adopt a one-sided psychological approach. Their embracement of psychoanalytic theories, which were neither provable nor refutable, led to many erroneous conclusions which predominated in literature for a considerable period with marked retardation of progress in this field.

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On the other hand, endocrinologists were inclined to be scornful of, or indifferent to, the psychological implications of the diseases they encountered at the clinics - leaning more to the physical to the neglect of the psychological aspects.

(iv) Above all, there seems to have been a failure to realise or acknowledge a psycho-neuro-endocrine vicious circle. Whether a disturbance arises primarily in the brain or in the endocrine system, the series of repercussions are bound to result in a vicious circle, and in the fully established state, it will be difficult to know where it all started. As Jacobi, quoted by Kraepelin (1962) said, "Physical processes, no matter how they differ, can influence the psyche. Conversely, the activities of the psyche can affect every conceivable physical function".

# CHAPTER II

## PART I: REVIEW OF THE LITERATURE ON HYPERTHYROIDISM AND ITS PSYCHIATRIC COMPONENTS.

### 1. Historical Considerations

The suspicion of a relationship between hyperthyroidism and emotional disturbance has been strong since the first description of a patient with the illness by Parry in 1802. The patient was a 21-year old female who was thrown out of a wheel chair in coming fast down a hill. She was unhurt but was very much frightened, and developed palpitations and various other 'nervous' symptoms. About a fortnight later she began to observe a swelling of her thyroid gland. Graves in his own publication, 33 years later in 1835, devoted a considerable part of his discussion to the possible relationship of the disease to hysterical conditions.

Patients /

Patients who suffered from the disease, and those who suffer from it in the present day, appeared very tense with a frightened expression. This led to the disease being given such names as 'frozen fright' and 'crystallised fear'. The clinical manifestations include restlessness, excessive sweating, and symptoms which to a large extent resemble severe neurotic states. It was therefore natural that it was generally regarded as a nervous condition. Charcot was reported to have described it as a neurosis. This general attitude continued until Mobius, in 1886, drew attention to the over-secretory nature of the thyroid gland in people who suffered from the disease.

Since the beginning of the 20th Century, there have been various views on the nature of the disease and the nervous phenomena which accompany it. Most physicians seemed to regard the disease as 'psychosomatic'*; and they saw its nervous components as a form of neurosis. There were assertions that people who suffered from the disease were always of a 'neurotic personality', and that the associated nervous phenomena was an expression of a 'thyroid constitution' (Moschcowitz 1930; Conrad 1934; Lidz 1949; Ham, Alexander and Carmichael 1961). Only a small proportion appeared to consider that dysfunction of the thyroid gland might tend to predispose to mental disorders (Dunlap and Moersch 1935; Robbins and Vinson 1960).

Two main groups of workers have therefore been identified in relation to the association between the emotions and thyroid function. The first group consists of those who hold to the 'psychosomatic' hypothesis that recurring or chronic emotional stress has a cumulative physiological effect and eventually may produce chronic reversible or irreversible organic dysfunction.

* This word is used here in the sense explained by Leigh (1968): "There are a particular group of disorders, <u>the psychosomatic disorders</u>, in which the relationship between psychosocial disturbance and the occurrence of illness is particularly clear".

The second group, which has fewer followers, takes a Kraepelin approach that the emotional disorder is due to the endocrine dysfunction. Recently, Kaplan and Hetrick (1962) have suggested what amounted to a third hypothesis. They proposed that where there was a history of antecedent trauma, the emotional disturbance found might be direct consequence of the trauma, (traumatic neurosis) and run a concurrent course with the hyperthyroidism even though the two were otherwise unrelated.

With regards to the first group, the tendency has been to over-emphasise the role of psychological factors in the aetiology of hyperthyroidism. The assessments were subjective, using clinical and anamnestic interview materials based on psychodynamic or psychoanalytic concepts. Psychological tests, when used, were usually of the projective types with unproven reliability and validity. Sufficient attention was not paid to the phenomenology of the psychopathology found in the patients, and longitudinal studies were few. Gibson (1962) made an extensive review of the literature on the studies belonging to this group. He concluded that there was no evidence that emotional stress could produce clinical hyperthyroidism in man, although such stress would inhibit temporarily thyroid activity in the experimental animal.

## 2. Definition and Concept of Hyperthyroidism

Hyperthyroidism is defined as functional overactivity of the thyroid gland irrespective of morphological changes in the gland. Clinically, it is best regarded as a syndrome. The circulating thyroid hormones are normal in quality but excessive in quantity.

It encompasses a number of diagnostic states including thyrotoxicosis, toxic goitre, exophthalmic goitre, Graves' disease, Parry's disease, Basedow's disease and toxic adenoma.

Strong (1968) has pointed out that, with the exception of toxic adenoma, the various names listed would appear to be synonyms for the same disorder.

Some clinicians would maintain however that it is possible to distinguish the classical Grave's disease from the other hyperthyroid states. Solomon (1969) argued that Grave's disease was more than just hyperthyroidism. He defined it as a multisystem disease consisting of one or more of four pathognomonic entities. These were:

1. Hyperthyroidism, due to diffuse thyroidal hyperplasia as distinguished from single or multiple hyperfunctioning adenomata.
2. Infiltrative Ophthalmopathy which, Solomon claimed, was absolutely unique to Grave's disease.
3. Infiltrative Dermopathy, consisting of localised pretibial myxoedema and also absolutely unique to Grave's disease.
4. Present of Long Acting Thyroid stimulating Substance (L.A.T.S.) in the serum above a certain level.

Factors 1, 2, and 3 did not necessarily follow each other but could run separate courses, suggesting that somewhat different factors might be producing each phenomenon. On the other hand, however, Rundle (1951) pointed out the extreme difficulty in trying to distinguish the classical Grave's disease. He admitted that there was overlapping between toxic goitre and Grave's disease, and that the relationship between the two was unclear. There was also an overlapping between Grave's disease and anxiety state, autonomic imbalance or neuro-circulatory asthenia.

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3. The Aetiology and Pathogenesis of Hyperthyroidism

The cause of hyperthyroidism is unknown. Thyrotoxicosis has a tendency to be familial, and to occur more frequently in the female sex - the female to male ratio being 8 to 1 (Strong op. cit). Frequently the patient's history suggests that the symptoms and signs of the disease were triggered off by psychological or physical stress. It seems that the pathogenesis of the disease might involve an auto-immune mechanism. The explanations available in text books attribute the glandular overactivity to the presence of an abnormal thyroid stimulator, L.A.T.S. (Strong op. cit). Irvine (1967) in a review of the developments in this field over a period of 10 years, quoted 80 per cent as the proportion of thyrotoxic patients in whose sera L.A.T.S. could be detected. He added that thyrotoxicosis, Hashimoto goitre, and primary atrophic hypothyroidism would seem to belong to a group of disorders which may involve tissues other than the thyroid such as the gastric mucosa, adrenal, or parathyroid. This group of diseases is characterised by:

(i) a genetic trait

(ii) a predominantly female incidence

(iii) histological appearance of lymphocytic infiltration in one or more tissues.

(iv) the occurence of organ specific antibodies.

He believed that there was a genetically determined defect in the immunological hoemeostasis of the individual. The fact that hypothyroidism is ten times more common amongst patients with Addison's disease than amongst the general population - Frederickson (1951) - is in keeping with Irvine's views.

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4. Clinical Features of Hyperthyroidism

The clinical features of hyperthyroidism consist of symptoms and signs which can be seen largely as the direct consequence of the overactivity of the gland. The most prominent of these are:

(a) Increased appetite.

(b) Persistent weight loss in spite of excessive eating.

(c) Sensitivity to warm environment

(d) Fine tremor of hand.

(e) Tachycardia - sleeping pulse rate of over 90 per minute.

(f) Palpitations which become especially severe after excitement or exertion.

(g) The thyroid gland itself may be palpable and a bruit may be heard on auscultation.

(h) The hands are warm and moist.

(i) There may be exophthalmos, lid lag, and lid retraction.

Patients with hyperthyroidism are often highly strung and over anxious. In some patients, the nervous symptoms dominate the clinical picture. The patient reports short temper, irritability, inability to relax mentally coupled with an urge to physical restlessness. Alternatively there may be a worsening of already existing psychiatric symptoms. Most, if not all, physicians treating patients with hyperthyroidism agree that it is a disease with psychological aspects of considerable importance. Wayne (1954) pointed out that about 60 per cent of hyperthyroid patients had nervous symptoms compared to 20 to 25 per cent of control subjects.

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There has been a tendency on the part of physicians to make the diagnosis of hyperthyroidism on the basis of the physical rather than the psychological symptoms and signs. This may be due to a number of factors. Most patients reach their doctor because of complaints in either their cardiovascular or neuromuscular systems (Brown 1969). A lesser proportion seek help because of the psychological symptoms. The conspicuous absence of psychiatric items - except "nervousness" - in the Wayne Index (Crooks et al 1959) was due to failure to find any symptom or sign sufficiently exclusive to hyperthyroidism to differentiate it from functional neurotic states. There has been little or no effort in the past to study, phenomenologically, the psychological symptoms occurring in hyperthyroidism. Gurney et al (1970) found that the inclusion of some psychiatric items in the Wayne Index markedly improved the efficiency of this index in discriminating psychoneurotic patients from hyperthyroid ones. They found no item which could distinguish the hyperthyroid patient from the psychoneurotic one.

The ultimate establishment and confirmation of a hyperthyroid state, however, relies on the use of laboratory quantitative tests of thyroid function. These tests can be divided into two main groups.

a. Those which measure the activity of the thyroid gland directly:-

(i) Ability to take up radio-active iodine, $I^{131}$ or $I^{132}$. $I^{131}$ uptake of a normal gland at 4-hrs. is between 20-40% with an uptake greater than 45% indicating overactivity.

(ii) /

(ii) Level of circulating thyroid hormone as measured by the amount of protein bound iodine (P.B.I.) in the blood. Normal values range from 4 to 8 microgram per 100 ml. serum.

b. Those tests which measure the effects of thyroid hormone on functions such as the in vitro uptake of radio-active triiodo thyronine by red cells ($T_3$ charcoal or resin uptake).

5. Classification of Hyperthyroidism

Of the three or four different classifications which exist, perhaps the simplest and easiest to understand is that which divides hyperthyroidism into the :

1. Primary

and

2. Secondary types.

The Term 'Primary Hyperthyroidism' is used when the disease develops simultaneously as the glandular enlargement or goitre formation (if there is one). This is subdivisible into (a) Grave's disease (exophthalmic goitre; toxic diffuse goitre; primary toxic goitre), and (b) Thryotoxicosis factitia (alimentary thyrotoxicosis; exogenous thyrotoxicosis). In the latter type, the disease is induced - apparently in an effort to lose weight - and should be considered in all cases with clear cut hyperthyroidism in which goitre is lacking. There is no increased radio-iodine uptake by the gland in spite of a high serum protein bound iodine, and a high urinary iodine.

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The term 'Secondary Hyperthyroidism' is used when the disease arises in a previously long standing goitre. In this case, the gland is nodular or lobulated, often asymmetrical in its enlargement and of greater size than is common in the primary type. It is this type of hyperthyroidism that is usually described as "toxic nodular goitre". It is subdivisible into:

(a) toxic adenoma, a hyperfunctioning ('hot') single nodule;

(b) toxic multinodular goitre, which itself may be subdivided into

(i) the endemic type which develops in a long standing colloid goitre, and

(ii) the sporadic type, which may develop in a simple goitre but is long continued and is due mainly to hyperfunctioning nodules in the gland.

## 6. The Emotional Disorders Associated with Hyperthyroidism

The most common emotional disturbances which have been described by both psychiatrists and physicians in association with hyperthyroidism are anxiety, apprehension, and irritability. Dunlap and Moersch (1935) examined a series of 143 hyperthyroid patients and found apprehension to be the most common psychic change. There was a varying degree of motor restlessness and nervous irritability in the patients. These mental reactions were considered to be similar to aggravated forms of psychoneurosis. In extreme cases the patients were liable to give evidence of mental confusion, delusions, and hallucinations. With these types of psychotic reactions, they found that no particular type could be considered characteristic. They found three types of psychotic reactions dominant: (a) toxic exhaustion psychosis, (b) acute delirium reaction, and (c) manic-depressive reaction.

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The first two of these constituted 91 per cent of the 134 patients with psychotic reactions. They then suggested that hyperthyroidism might act as a definite aetiologic factor in the production of the mental manifestations in these two groups.

It is not often that the emotional disturbance in hyperthyroidism assumes psychotic proportions as was found in the study by Dunlap and Moersch. Johnson (1928) felt that psychosis was infrequently associated with the disease, and that when the two co-existed, it was a pre-existent psychosis that was aggravated or re-activated rather than caused afresh. Ginsberg (1932) however thought that the co-occurrence between hyperthyroidism and psychosis was more than mere coincidence. The views expressed by Johnson have been supported by the findings of other workers. Foss and Jackson (1924) observed that pronounced maniacal and paranoid psychoses might occur with thyroid disease, but such occurrences were rare and as a rule seen only when there was a "psychopathic heredity". They studied 800 patients admitted to a general hospital, and found only a very small proportion of those with hyperthyroidism - less than one per cent - showed evidence of mental aberration. Only two patients had mild excitement and transient mania. Unfortunately these workers did not quote the exact number of the hyperthyroid patients in the population studied. More recently, Greer and Parsons (1968) have also reported the infrequent association between hyperthyroidism and psychosis. It would seem therefore that the sample reported by Dunlap and Moersch was an atypical one.

Artunkal and Togrol (1964) studied 20 female thyrotoxic patients of middle socio-economic background. They were matched for age, sex, socio-economic status and educational background with normal controls. Psychological examination was done before, and at varying intervals of between 4 and 12 months after treatment. Using the Minnesota Multiphasic Personality Inventory (M.M.P.I.) they found the thyrotoxic group to have a high elevation on the paranoia scale, and a relatively smaller elevation on the depression and schizophrenic scales. After treatment there was some reduction on the paranoia scores but the depression scores appeared to persist at the same level.

Robbins and Vinson (op. cit) found the psychological symptoms in their sample of 10 thyrotoxic patients to be sleep disturbance, nervousness, irritability, and depression. All these were abolished by treatment.

Whybrow, Prange and Treadway (1969) examined a group of 10 hyperthyroid patients attending a general hospital clinic. Fatigue, anxiety and irritability were the most frequent complaints. Only two patients complained of depression; paranoid symptoms were found in two patients, one of whom had visual hallucinations. Only one patient was severely disturbed enough to be referred for psychiatric management. On the M.M.P.I., the profile was elevated and suggested "a hysteroid elaboration of somatic complaints". A reduction of psychiatric symptomatology was found in seven of the nine patients retested. Somatic concern, anxiety, emotional withdrawal, conceptual disorganisation and motor tension were the scales showing greatest and most consistent reduction.

Although emotional disturbance is more often described in association with thyrotoxicosis and classical Grave's Disease, there is no evidence that it is confined to this type of hyperthyroidism.

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In experimental and self-induced states of hyperthyroidism (thyrotoxicosis factilia), a fairly similar pattern of psychiatric symptoms have been observed irrespective of the personality of the patient (man or animal).

Karnosh and Williams (1934) described the case of a female patient who had been consuming large amounts of thyroid extracts in order to treat her obesity. The exact quantity consumed was not known. She was later admitted in a state of toxic delirium, agitation, noisiness and talkativeness. Immediate improvement followed cessation of the thyroid therapy.

Thompson (1945) reported the case of a physician who administered 80-120 gm. of thyroid extract to himself daily for a period of over 12 months. He was admitted to hospital with the physical signs of hyperthyroidism, including cardiac failure. The psychic manifestations were also those of toxic delirium. Cessation of the drug relieved the toxic symptomatology and unmasked an underlying depression. He had taken the large doses of thyroid extract in an attempt to commit suicide.

Aoki et al (1967) in an experiment to study the cardiovascular effects of thyroid hormones, administered varying doses of thyroid hormones by injection to male volunteers. He reported "nervousness", tremor, agitation, and increased irritability as being prominent symptoms in the majority of his subjects especially during the time they were receiving 500 mg. of tri-iodothyromine per day.

It would seem therefore that what is important is the quantity of thyroid hormones circulating in the individual rather than the cause of, or the morphological changes in the gland.

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It is apparent from the studies reviewed that no psychological disturbance could be described as typical of hyperthyroidism. Anxiety, apprehension and irritability appear to be the most common disturbance. However the variation in the terminology used to describe an apparently similar psychic disturbance would suggest that it is probably not identical to the morbid anxiety encountered in neurotic anxiety states. In hyperthyroidism, the anxiety appears to be physiologically dependent on the endocrine abnormality, and to lack the qualities associated with morbid neurotic anxiety. It is possible that "anxiety" as it is found in hyperthyroidism, is a primarily sensational phenomenon, perceived and interpreted in the light of the patient's previous experience. The affective tone might be a secondary reaction to, or an overlay on, the primary state. This notion seems to be reinforced by the little evidence available from previous psychophysiological studies.

## 7. Psychophysiological Studies of Hyperthyroidism

It was possible to trace two relevant reports in the literature. Both were from the same group of workers, and were apparently reporting the same experiment.

Alexander et al (1961) studied seven untreated hyperthyroid patients, seven treated patients, and five controls matched for age and sex. The workers were interested in identifying films most appropriate for inducing stress in various diagnostic groups of patients. They exposed their subjects to the film "Wages of Fear" and monitored various psychophysiological indices which included the skin resistence, finger pulse volume, and the serum protein bound-iodine levels.

During /

During the film exposure, they found a progressive decrease in skin resistence which was greater and highly significant in the untreated hyperthyroid patients compared to the other two groups.

Flagg et al (1965) were able to extend the study by Alexander et al to a total of 43 untreated hyperthyroid patients and 31 control subjects. They compared the psychophysiological responses to neutral and stressful films. The variables they measured included skin resistance level, heart rate, respiration rate, and finger pulse volume. They found that the untreated hyperthyroid patients had significantly greater reactions on two of the variables (skin resistance and heart rate). In contrast the control subjects and the treated hyperthyroid subjects showed minimal psychophysiological reactions regardless of which film (stressor, non-stressor) they were watching.

PART II: REVIEW OF THE LITERATURE ON THE METHODOLOGICAL ASPECTS OF THIS STUDY.

## (A) The Assessment of Patterns of Feelings and General Psychiatric Morbidity (Use of the Cornell Medical Index - C.M.I.)

The Cornell Medical Index is a questionnaire consisting of 195 questions grouped into 18 sections designated by the alphabetical letters A to R. Sections A to L (140 questions) deal mainly with physical symptoms covering all the bodily systems. Sections M to R (55 questions) consist mainly of psychological questions. The questions in the Index are of four types relating to:

(i) bodily symptoms,

(ii) past illnesses,

(iii) family history,

(iv) behaviour (mood or feeling).

The Index was originally designed as an adjunct to medical out-patients consultations (Brodman et al 1949).

Since /

Since its development, it has been used as a diagnostic instrument (Brodman et al 1952), and for the prediction of psychosomatic and psychiatric disabilities in army training (Brodman et al 1954), and during university studies (Coldbeck-Meenan 1966).

The C.M.I., in a British population, was first used in a study of psychiatric morbidity in adult asthmatics by Leigh and Marley in 1956. They studied four groups of subjects consisting of

(a) a group of asthmatics attending a general physician at a general hospital;

(b) a group of asthmatics attending for psychiatric treatment at the Maudsley Hospital in London;

(c) a group of neurotic patients attending a psychiatrist at the Maudsley Hospital;

(d) a group of workers in a large London department store.

This last group constituted the sample of normal (healthy) subjects. Only the scores on the M-R scales of the Index were analysed. No significant difference was found between the asthmatics being seen by the psychiatrist and the neurotics. The asthmatics attending the general physician scored less than both the neurotics and the Maudsley asthmatics. All the patient-groups had higher scores than the normal (healthy) subjects.

Brodman et al (1952) suggested that emotional disorder should be suspected if any of the following were present in the C.M.I. :

(a) /

(a) 30 or more "Yes" responses in the whole questionnaire;

(b) 3 or more questions answered both "Yes" and "No";

(c) 6 or more questions omitted;

(d) 3 or more questions with remarks or alterations;

(e) 3 or more "Yes" responses in the sections dealing with psychological symptoms i.e. the M to R sections.

Studies in the British population have, however, shown that, with the last criterion, a score of 10 "Yes" or more on the M - R sections formed a more suitable cut-off point for differentiating neurotic from normal subjects with minimum misclassification (Culpan et al, 1960; Brown and Fry, 1962; Knox, 1963). The mean scores obtained for various population groups are shown in Table 1.1.

Culpan et al (op. cit.) demonstrated that the Brodman's critical score of 3 on the M-R scales was obtained by a high proportion of "normal" subjects. Using a critical score of 10, there was only a 20 per cent misclassification in the normal, and 24 per cent in the neurotic subjects.

Brown and Fry (op. cit.) conducted an investigation to see if the C.M.I. would correctly identify those patients who had been given the diagnosis of 'neurosis' by their own general practitioner. They gave the Index to a total of 183 patients, representing a one-in-ten sample of those attending the practice. Of the 170 patients who completed the Index, 30 had been given the diagnosis of 'neurosis' by their general practitioner. In addition a group of 32 patients who were considered by their general practitioner to be neurotic completed the Index. Thus, they were able to obtain scores for a total of 62 neurotic patients, and 140 patients without evidence of neurotic disturbance.

They /

| GROUPS | | Sample Size | Scales M - R | Scales Total |
|---|---|---|---|---|
| 1. Normal (healthy) populations* | | | | |
| | Males | 48 | 2.8 | 11.0 |
| | Females | 56 | 6.9 | 20.8 |
| 2. General Hospital Out-Patients Populations* | | | | |
| (a) Medical Clinics | - Males | 34 | 3.9 | 21.4 |
| | - Females | 61 | 8.6 | 32.6 |
| (b) Surgical Clinics | - Males | 26 | 3.9 | 20.4 |
| | - Females | 55 | 9.5 | 31.2 |
| 3. Psychiatrically Ill Populations+ | | | | |
| (a) Psychiatric hospital outpatients | | | | |
| | - Males | 28 | 15.8 | 40.2 |
| | - Females | 38 | 20.2 | 47.1 |
| (b) Persons identified as 'Neurotic' in a random sample of patients attending a general practice | | | | |
| | - Males | 9 | 10.0 | 29.8 |
| | - Females | 21 | 12.8 | 34.4 |
| (c) Selected samples of neurotic patients in a general practice | - Males | 10 | 17.7 | 41.3 |
| | - Females | 22 | 18.1 | 47.6 |

*Culpan, Davies and Oppenheim (1960); +Brown and Fry (1962)

Table 1.1 Showing the published mean scores on the Cornell Medical Index (C.M.I.) for various groups.

They found that a cut-off point (i.e. critical score) of 10 on the M-R scales, or 30 on the total (entire) scale separated the neurotics from the non-neurotics very adequately. They found mean M-R scores of 3.4 (males) and 7.0 (females) for the non-neurotic patients, and 10.0, 17.7 (males) and 12.8, 18.1 (females) for the two groups of the neurotic patients. See Table 1.1 (3b,c.). They concluded that the C.M.I. was of value in picking out emotionally disturbed patients. It did not give a 100 per cent differentiation of neurotic patients from normal subjects, but they were doubtful if there were other questionnaires or screening devices which could give such a high differentiation.

Knox (op. cit.) used the Index to study psychiatric illness associated with mitral surgery. He compared the scores on the M-R and the total scales of the Index with an assessment of psychiatric morbidity made by psychiatric interviewing. He also used cut-off points of 10 on the M-R, and 30 on the total scales, and obtained highly significant differentiation between patients who were psychiatrically disturbed post-operatively, and those who were not ("well-adjusted patients").

## (B) The Assessment of Anxiety

Since anxiety is a subjective feeling state, there is no way of measuring it directly. The extent to which an individual is anxious may be simply assessed by finding an adjective which best describes his state of mind. Buss (1966) has listed a series of adjectives which describe the different stages on a continuum from normal (non-anxious) to the most anxious level of feeling :

nonchalant
calm
composed
uneasy
fretful
tense
apprehensive
tremulous
agitated
panicky
terrified.

Alternatively /

Alternatively anxiety may be assessed by observing its concomitants or indicants. Aitken and Zealley (1970) have produced an extensive table of these concomitants, many of which are measurable. These are reproduced below :-

| | |
|---|---|
| 1. Changes in thinking | Worry, dread and apprehension.<br>Reduced concentration and field of attention.<br>Distractibility and forgetfulness.<br>Irritability and depression.<br>Insomnia and nightmares.<br>Perceptual disturbance, such as depersonalisation. |
| 2. Changes in physiological activity. | |
| (a) Motor activity | Muscular tension and trembling.<br>Restlessness and fidgeting.<br>Incoordination and impaired performance.<br>Startle reactions.<br>"Freezing". |
| (b) Other somatic functions | Flushing and sweating.<br>Dry mouth and anorexia.<br>Choking feelings as if lump in throat.<br>Rapid breathing, and sometimes hyperventilation.<br>Palpitations, tachycardia, and hypertension.<br>Headache, fatigue, weakness and fainting.<br>Dyspepsia and diarrhoea.<br>Urgency and frequency of micturation.<br>Impotence.<br>Menstrual disturbance. |

Table 1.2 The psychological and physiological concomitants of anxiety.

Thus /

Thus two main methods have emerged in the attempt to measure indicants of anxiety. These are psychometric and physiological methods respectively.

1. Psychometric Scales.

An assessment of the level of anxiety felt by a patient may be made by asking him to rate himself on an inventory of symptoms. The Taylor Manifest Anxiety Scale (Taylor, 1953) is an example of such an inventory. The patient can also communicate his level of anxiety on a Visual Analogue Scale (Aitken 1969). Many of the shortcomings encountered with subjective techniques of assessments are thus bound to perpetuate themselves in the rating scales.

(a) The Taylor Manifest Anxiety Scale (T.M.A.S.) This consists of statements to which the subject may answer "True" or "False". A scoring key indicates those responses which, if identically marked, should be counted to give the total score for the patient. According to Taylor, the mean score for a total of 1,971 healthy students was 14.56. This is comparable with the mean of 14.0 (standard deviation 7.9) obtained for a sample of 60 normal British subjects (Kelly and Walter 1969). The 50th percentile fell at 13, the 80th at about 21, and the 20th at 7. The test-retest reliability at three weeks was 0.89, thus showing the scale to have a high degree of consistency over time.

The T.M.A.S. was developed from the Minnesota Multiphasic Personality Inventory (M.M.P.I.). The title of the publication in which Taylor described the test was "A Personality Scale of Manifest Anxiety". She declared at the beginning that its construction was based on a clinical definition of anxiety.

It /

It would therefore appear that in spite of the misleading title, the test was designed to measure anxiety as a state and not as a trait. Taylor herself gave some preliminary results from a study to determine the relationship between the scale measures and clinical assessment of anxiety. The figures showed that the median score (34) for a psychiatric patient-population fell at the 98.8th percentile of normal subjects. The scale has been shown in British subjects to discriminate highly between normal and psychiatric populations. (Kelly 1966; Kelly and Walter op.cit.).

(b) The Visual Analogue Scale (V.A.S.) This scale employs a line, 100mm. in length, with its ends defined as representing the extremes of the subjective experience (for example, anxiety) under investigation. The line thus represents a simple analogue on which the patient can rate the intensity of his feeling. Since moods vary in a continuous fashion, this method of rating seems more logical than other ratings which make use of artificial categories (e.g. mild, moderate, severe) or dichotomous answers (True - False). Since measurements of the patients' ratings can be made to the nearest millimeter, the scale provides a sufficiently large number of categories to allow it to be considered a continuum; and so the scores meet the assumptions necessary for parametric statistics and other tests such as variability in response (see page63 ). In addition much can be learned from visual inspection of the scores. (Zealley and Aitken 1969).

2. Psychophysiological Assessments.

This approach centres on certain physiological features of anxiety (Table 1.2), the majority of which are autonomic.

Two psychophysiological measures which were used in the assessment of mood in this study are :

(a) Palmar Skin Conductance measures, which consist of the

(i) basal level of skin conductance;

(ii) frequency of spontaneous fluctuations in skin conductance;

(iii) the magnitude of the psycho-galvanic reflex to a standard stimulus;

(iv) the rate of habituation of such reflexes to repeated presentation of the same stimulus.

(b) Cardiovascular measures :

(i) resting heart rate

(ii) resting forearm blood flow.

All these measures, except perhaps the heart rate, have shown promise in the psychophysiological assessment of anxious patients.

What the psychophysiological methods actually measure is the degree of arousal of the individual. Malmo (1957, 1959) had postulated that patients with anxiety states were chronically hyperaroused. But arousal may also be increased by anger, ecstasy, or a sexual stimulus. Abnormal psychophysiological measures may, therefore, not always indicate the presence of an abnormal level of anxiety unless the latter is known - or suspected - to be present as well.

(a) Palmar Skin Conductance

(i) Level. This is an indirect measure of sweat gland activity. Kuno (1956) has shown that there are two kinds of human perspiration: thermo-regulatory and emotional.

Both /

Both are mediated by eccrine sweat glands but in different areas. Thermo-regulatory sweating occurs continuously all over the body except in the skin of the palms and soles. Emotional sweating takes place mainly in the palms and soles. The electrical conductance of the skin has been shown to be dependent on the number of active sweat glands (Martin and Venables 1964; Wilcott 1962). The palms and the soles have the densest concentration of sweat glands, and therefore a lower resistance, than any other area of the body. It would appear, however, from the review of the literature, that above about 75°F, significant correlations may be obtained between palmar sweating and temperature in some, but not all, groups of subjects.

Darrow (1970) has maintained that the peripheral mechanism of the psycho-galvanic reflex (P.G.R.) was simple. It did not depend primarily upon the emergence of sweat, but rather on the pre-secretory activity of the sweat gland cell membranes. The peripheral neuro-physiological mechanism, as described by Darrow, seems to be "a sequential phenomenon involving, first, neural effector excitations of epidermal tissue, including but not limited to the superficial tissue of the sweat glands, and second, if this neural excitation continues, elaboration of acetylcholine with consequent sweat secretion" (Gullickson and Darrow 1968). Sympathectomy abolishes the P.G.R., and people with congenital absence of sweat glands have a high skin resistance and no P.G.R.

In general, resting levels of conductance are higher in anxious than in normal subjects.

(ii) Spontaneous fluctuations. The frequency of spontaneous fluctuations in skin conductance is known to be a sensitive index of arousal.

The frequency was increased during phantasies of anxiety-provoking situations (Marks et al 1969), in panic attacks (Aitken et al 1969), in visualisation of stressful films, and on exposure to recorded verbal stimuli consisting of emotionally charged words (Silverman et al 1959). Spontaneous fluctuations were absent during an episode of depersonalisation (Lader 1969), and were generally more frequent in a group of psychiatric hospital patients suffering from anxiety states when compared with a control group of normal subjects (Lader 1964).

Experiments by Greiner and Burch (1955) and Lader and Wing (1964) have shown that when a subject was given sedative drugs in fractionated doses, the number of spontaneous fluctuations per unit time decreased as he became more sedated. When sleep was reached, no spontaneous fluctuations were obtained. At the same time, the basal level of conductance decreased. Greiner and Burch also demonstrated that administration of a stimulant drug increased the frequency of spontaneous fluctuations.

(iii) The Psycho-galvanic reflex (P.G.R.) and its habituation to a repeated stimulus. The P.G.R. consists of a rapid increase followed by a slower recovery in the electrical conductance of the skin in response to a stimulus. The phenomenon was first observed by Fere in 1888, the term being coined by Veraguth in 1907 to describe it. Synonyms include the galvanic skin response (G.S.R.) and the skin conductance response (S.C.R.)

The P.G.R. is a form of the orienting reflex described by Sokolov (1963). It is a non-specific reflex initiated by any increase or decrease or qualitative change of a stimulus, and is independent of the modality of the stimulating agent.

It /

It is also subject to extinction or habituation on repeated presentation of the stimulus. Sokolov pointed out that the orienting reflex was not the same as the adaptive reflex or the defensive reflex, and that it could be differentiated from these two. The adaptive reflex is the reflex connected with the direction of change of the stimulus. An example of the adaptive reflex is the pupillary reflex in which the degree of pupillary constriction depends on the intensity of light. The defensive reflex on the other hand is a general response of the organism when the stimulus is too strong for normal conditioning. It would appear from some recent studies that the psycho-galvanic reflex is probably of crucial importance in the "registration" of events experienced by the individual (Bagshaw et al 1968).

The rate of habituation of the psycho-galvanic reflex to repeated presentation of a standard stimulus (100Hz tone at 100dB of 1 second duration) has been shown to be much higher in normal subjects when compared with patients suffering from anxiety state (Lader and Wing 1964). Lader (1964) found that the habituation followed an exponential course. He therefore computed the regression of the magnitudes of the psycho-galvanic reflexes on the log transformation of stimulus number. This enabled him to obtain a linear relationship between the two variables. The rate of habituation by a subject, measured by the slope of the regression curve, was assessed by an analysis of variance (Snedecor 1956). When the slope was significantly greater than zero, the subject was regarded as having habituated. The rate of habituation was increased by amylobarbitone or chlordiazepoxide in sedative doses (Lader and Wing 1966), and patients with agitated depression

habituated /

habituated much less rapidly than those with retarded depression (Lader and Wing 1970). Patients with hysterical neurosis (with "la belle indifference" rather than overt anxiety) also failed to habituate when repeatedly presented with a standard stimulus (Lader and Sartorius 1968).

Thus, habituation of P.G.R. has a number of useful applications in psychiatric research. It has been shown to identify patients with anxiety neurosis even when this is masked, as in the "la belle indifference" appearance of the hysteric, or as in depressive illness. It also promises to be a useful tool in bio-assay of sedative drugs. When an absolute score of habituation was derived and used in serial tests, it was shown that this score did not vary significantly between successive tests or in relation to the length of interval between the tests (Montagu 1963). This suggests that it might prove to be a reliable and valuable index in the longitudinal study of mental illness and in therapeutic trials.

(iv) The neurophysiological basis of the psycho-galvanic reflex and its habituation. This remains to be fully clarified. Bilateral ablation of the amygdala has been shown to depress the reflex markedly in monkeys (Bagshaw et al 1965, 1968b). Bagshaw et al (op. cit.) presented their experimental animals with a tone of either 1000Hz at 77dB, or 1500Hz at 81dB. Each tone lasted two seconds and was presented at irregular intervals. Habituation was deemed to have occurred when no reflex could be elicited with four consecutive presentations of the tone. They also found that hippocampectomy and lesions of the infero-temporal isocortex had no effect on the reflex. Kimble et al (1965), using the same technique, found that lesions of the lateral frontal cortex depressed

the reflex whereas medial-frontal-anterior cingulate lesions did not. The effect of lesions of the frontal cortex in man has been described by Luria and Homskaya (1963). They studied one patient with a frontal meningioma and found gross disturbances of the plethysmograph and the P.G.R. Background skin conductance level was flat with only an occasional spontaneous fluctuation. The P.G.R. was weak, and could only be provoked by stimuli of great intensity.

Wang (1955) has demonstrated the involvement of the brainstem reticular formation. Working on cats under anaesthesia, he found that elimination of the facilitatory influences of the reticular formation through transection of the brain stem at the intercollicular level greatly reduced the intensity of the reflex. Stimulation of the facilitatory portion with a weak current produced a reversal of the above effect. The inhibitory portions of the reticular formation produced exactly opposite effects. Habituation to acoustic stimuli in the cochlear nucleus is similarly influenced by the activity of the brain stem reticular formation (Hernandez-Peon and Scherrer 1955; Hernandez-Peon et al 1956; Bagshaw et al 1965).

It would seem therefore that the P.G.R. and its habituation require the functional integrity of the brain stem reticular formation, the amygdala, and the frontal cortex.

(v) <u>The Unit of Measurement of the Skin Conductance and the P.G.R.</u> Many investigations in psychophysiology require estimates of the between-groups and within-groups differences with respect to the amount of reaction shown by a given effector system, or a group of effectors.

Sometimes /

Sometimes it is necessary to compare the responses of an individual to various stimuli (within-subject comparison). The magnitude of response would be expected to be the difference between level of activity before stimulation, and after. It is in this respect that the application of the Law of Initial Value is of importance in psychophysiology. This law, which was formulated by Wilder (1957), states that as the level of function of an organ rises, the size of response to a given function-increasing stimulus diminishes. It is argued, for example, that an increase in heart rate from, say, 70 to 80 beats per minute, is not physiologically equivalent to an increase from 80 to 90 beats per minute though the arithmetic difference is 10 beats per minute in both cases. Therefore in order to obtain "average" responses or to compare magnitudes of response within subject, some adjustments must be made to eliminate or equate the influence of the pre-stimulus level on the response magnitude.

In addition to satisfying the requirements of the Law of Initial Value, any unit of measurement must enable the data collected to be suitable for analysis by the usual parametric statistical techniques. This means that the data should possess the following characteristics :-

1. additivity and other properties expected of units of measurement on an ordinal scale;
2. normal distribution;
3. homogeneity of variance;
4. independence of the means and variances;
5. randomness.

Lacey, who has made an extensive investigation of the importance of the Law of Initial Value in psychophysiological assessments of autonomic responses, pointed out that individuals differed greatly in the extent to which the Law applied. The degree of dependence on pre-stimulus levels of activity varied from person to person, from one physiological variable to another, and from time to time (Lacey 1956; Lacey and Lacey 1962).

In meeting the requirements of the Law of Initial Value, there has been a tendency on the part of investigators to select a unit of measurement of responses which is independent of the pre-stimulus level. Such units suffer from one setback of biological importance. Failure to take the baseline into account ignores the fact of homeostatic processes in operation.

Haggard (1949a; 1949b), in an empirical study, compared four units of measurement of the P.G.R. namely,

(a) the change in resistance;

(b) the change in conductance;

(c) the log resistance change, i.e. log of (a) ;

(d) the log conductance change, i.e. log of (b).

He concluded that the log conductance change best satisfied the criteria required of the ideal unit of measurement. The four measures could not be used interchangeably because they tended to yield highly significant differences when applied to the same original scores or data.

Lacey and Siegel (1949) were more concerned with finding a unit of measurement which would be independent of the basal level so that a valid comparison of P.G.R.'s could be made between subjects on differing basal levels.

In /

In addition, such a unit would also satisfy the other criteria on page They examined eight units which included -

(a) change in resistance, R;

(b) change in conductance, C;

(c) percentage change in R;

(d) percentage change in C;

(e) change in log R;

(f) change in log C;

(g) log change in C.

The distribution of scores in terms of each unit was examined first for independence of basal level, and second - if satisfactory in this respect - for normality of distribution. They found that only change in conductance and log change in conductance satisfied their criteria.

Darrow (1964) approached the problem from a completely different angle. He was more interested in identifying the unit of measurement which best reflected the physiological activity of the sweat glands. He came to the conclusion that conductance was more appropriate than resistance as the unit of measurement. This has been supported by Lader's argument based on the arrangement of sweat glands in parallel (Lader 1970). Darrow postulated that for relating the physiological measures to psychological activity, the logarithm of the conductance would give a still better index. This is in accordance with the Weber-Fechner law.

(b) Cardiovascular Measures

(i) Forearm Muscle Blood Flow. The use of forearm blood flow as an index of arousal and mental activity was only developed in recent years by Kelly (1966).

Prior /

Prior to this, various workers have noticed that a relationship existed between the mental state of an individual and the rate of blood flow in his forearm (Hewlett et al 1909; Grant et al 1938); their observations were not however pursued. In 1940, Abramson and Ferris made a similar observation and studied it in more detail. They found that mental arithmetic produced an increase in forearm blood flow due to vasodilatation of the vessels in the forearm muscle. This observation has been confirmed by Brod et al (1959), Barcroft et al (1960), Harper et al (1965), and Kelly (1966).

Using venous occlusion plethysmography, Kelly (1966) has demonstrated the discriminant value of forearm blood flow in identifying patients with anxiety states from normals. The mean basal forearm blood flow for his group of normal subjects was 2.19ml of blood/100ml of forearm/min., while that for a group of 'mixed neurotics" was 2.31ml/100ml/min., and for patients with anxiety states was 4.78ml/100ml/min. It is however important to note that Kelly's group of anxiety patients consisted of patients with chronic anxiety. He included a patient only if the patient had had symptoms daily, and regular panic attacks for 2 years. It might therefore mean that the basal forearm blood flow is only of value in identifying the severely hyperaroused 'neurotic', and may not be of much use in acute and less severe forms of neurosis. It has, however, been shown to be a reliable and stable index with a test-retest correlation of 0.90. It correlated ($P<0.001$) with anxiety self-rating ($r = 0.24$), and with the Taylor Manifest Anxiety Scale ($r = 0.21$) (Kelly, 1967). Although the correlations were highly significant, it can be observed that they were rather low.

Mental /

Mental arithmetic increased the blood flow in all groups, the level being increased by as much as 312 per cent. Kelly found the increase to be highest in normals and least in anxious patients. Since the stress values were produced by a specific anxiety-provoking stimulus, Kelly suggested that this parameter might be a useful measure of situational (phobic) anxiety.

(ii) Heart Rate (H.R.)

Studies concerning heart rate changes and emotional states are legion, but few provide precise data. Most studies involved measuring the heart rate during psychiatric interviews or psychotherapy sessions. Much information, gained in the study of heart rate as an index of arousal derives from analysis of changes in the heart rate due to the effects of stress or drugs.

Resting heart rate, although one of the simplest psychophysiological indices to record, can be most difficult to interpret. It is easily influenced by a host of factors, including exertion and respiration. Since anxiety is likely to involve some muscular activity (e.g. muscle tension), changes in heart rate could only be taken as a crude index of alteration in level of anxiety.

The heart rate has been used in psychology as an indicant of emotion (Lacey et al 1955), and as a dependent variable in the study of classical conditioning (Shearn 1961). When groups of subjects were given mental arithmetic to perform, their mean heart rate rose by between 14 and 33 per cent (Kelly 1966). Malmo and Shagass (1949) found that psychiatric patients with functional heart complaints had a significantly higher heart rate than those without.

Altschule (1953) has reviewed the literature on this subject. He came to the conclusion that the heart rate was normal or only slightly accelerated in patients with "neurosis". In general, they did not differ from normal subjects.

# CHAPTER III

## METHOD

1. Sampling :

The subjects included in this study were recruited from among patients referred to the outpatient endocrine clinics at the Western General Hospital, and the Royal Infirmary of Edinburgh. They were all referred to the clinics suspected of suffering from hyperthyroidism. They all complained of symptoms commonly found in this disease, typically common symptoms consisting of "nervousness", palpitations, tremor of the hands, and excessive sweating.

Those confirmed by laboratory investigations to be hyperthyroid formed the proband group. Those whose tests returned normal, and were not suffering from any other physical illness, formed the comparison group; to all intent and purpose, these were patients with "functional" or psychoneurotic symptoms simulating hyperthyroidism. See Table 2.0.

All consecutive referrals, confirmed to be hyperthyroid, were approached to participate on a voluntary basis if, in addition, they satisfied the following criteria.

(a) An age of between 20 and 65 years.

(b) Absence of pregnancy or any form of serious physical illness other than hyperthyroidism.

(c) Residence within the city boundaries of Edinburgh.

The /

| Test | Hyperthyroid Group N = 20 | | Comparison Group N = 20 | |
|---|---|---|---|---|
| | Mean | s.d. | Mean | s.d. |
| Protein-bound Iodine (P.B.I.) in micrograms per 100 ml. | 13.5 | 2.7 | 6.6 | 1.5 |
| 4-hour $I^{131}$ Uptake | 59.0% | 17.6 | 17.7 | 7.0 |

Table 2.0 Showing the results of the thyroid function tests before treatment was started.
The mean P.B.I. for the hyperthyroid group after 12 weeks was 6.6 micrograms per 100ml (s.d. = 3.2).
Ten Comparison Group subjects - also investigated - had a mean P.B.I. of 7.4 micrograms per 100ml (s.d. = 1.8).

The last criterion was included in order to avoid attrition due to transport difficulties likely to be encountered were the patient to come from further afield. Of the total number of confirmed hyperthyroid patients approached to participate, 26 per cent refused outright at the beginning and 6 per cent withdrew at various stages of the study. The 20 patients reported about in this study thus represent 68 per cent of all those originally approached.

Patients forming the comparison group were screened and matched as closely as possible with the patients in the proband group for age and socio-economic status. This was achieved by including a patient in the comparison group only if her age was within a range of $\pm$ 5 years of the age of, and her social class was in addition deemed to match that of, the respective hyperthyroid subject. Table 2.1 shows the age distribution for the two groups of hyperthyroid patients and comparison patients. To match for social class, it was necessary to divide the five social classes into two main groups; social classes I and II on the one hand, and social classes III to V on the other. Two patients were considered matched if both had their social classes in the same group. Table 2.2 shows the social class distribution for the proband and the comparison groups.

Although attempts were made to match for sex and marital status, it was not possible to achieve exact matching in each case. Table 2.3 and Table 2.4 show the sex and marital status distribution in both groups. It can be seen that although not all the male hyperthyroid patients could be matched, there was no significant differences in the sex distribution of the two groups.

Similarly /

| | Hyperthyroid Group N = 20 | | Comparison Group N = 20 | | Significance of |
|---|---|---|---|---|---|
| | Mean | s.d. | Mean | s.d. | Difference* |
| Age | 38.6 | 12.3 | 37.6 | 11.3 | P = N.S. |

*t test

Table 2.1 Showing the age distribution of the hyperthyroid and comparison groups.

| | Hyperthyroid Group | Comparison Group |
|---|---|---|
| Social Class: I - II | 10 | 9 |
| III - V | 10 | 11 |

$X^2 = 0.0001$; d.f. = 1; P = N.S.

Table 2.2. Showing the social class distribution of the hyperthyroid and comparison groups.

| | Male | Female | Total |
|---|---|---|---|
| Hyperthyroid Group | 4 | 16 | 20 |
| Comparison Group | 2 | 18 | 20 |

$X^2$ (With Yate's Correction) = 0.19; d.f.=1; P = N.S.

Table 2.3 Showing the sex distribution of the hyperthyroid and comparison groups.

| | Ever Married* | Never Married | Total |
|---|---|---|---|
| Hyperthyroid Group | 16 | 4 | 20 |
| Comparison Group | 17 | 3 | 20 |

* Included: presently married, separated, divorced, or widowed.

$X^2$ (With Yate's correction) = 0.0001; d.f.=1; P = N.S.

Table 2.4 Showing distribution of the marital status for the hyperthyroid and comparison groups.

Similarly it was not possible to match one unmarried (never-been-married) hyperthyroid patient, but this difference was not found to be statistically significant either.

The design of the study demanded that the hyperthyroid patients should receive no psychotropic drugs - or other forms of psychiatric treatment beyond the possible effects of the contacts with the experimenter. Such contacts were kept at the minimum sufficient for the tests to be carried out. An identical management - that no psychiatric treatment be given - was also considered necessary for the patients who formed the comparison group. This would have enabled the two groups to differ in only one major respect - i.e. diagnosis. But the severity of the distress communicated by some of the comparison group patients indicated a need for the urgent relief of their symptoms. Therefore, in the analyses of the effect of treatment, the comparison group was divided into two sub-groups consisting of :-

(a) 10 patients who had psychotropic drugs for their symptoms - referred to in this thesis as 'treated comparison group'.

(b) 10 patients who had no drugs - referred to as 'untreated comparison group'.

The age, sex, marital status, and social class distributions of both sub-groups were examined; and no statistically significant difference was observed between them, nor between each sub-group and the hyperthyroid group.

## 2. The Laboratory

The Psychophysiology Laboratory consists of a larger room in which the recording instruments were set up, and a smaller adjoining experimental cubicle where the subject sat during each experiment. The experimenter remained in the larger room whenever recording was in progress, but he could communicate with the subject - if necessary - through a high quality intercom system.

The experimental cubicle was a controlled-environment; it was air conditioned and sound-attenuated with tape-recording facilities. The temperature in this room was thermostatically maintained at 22-23°C thus ensuring that it was below the critical temperature of 24°C (75°F) above which, according to Venables (1955), significant correlations may be obtained between environmental temperature and skin-resistance level. No humidifier was used, but the air in the cubicle was usually damp.

Fig. 2.1 is a diagrammatical illustration of the arrangement of, and the connections between, the different equipments in the Laboratory.

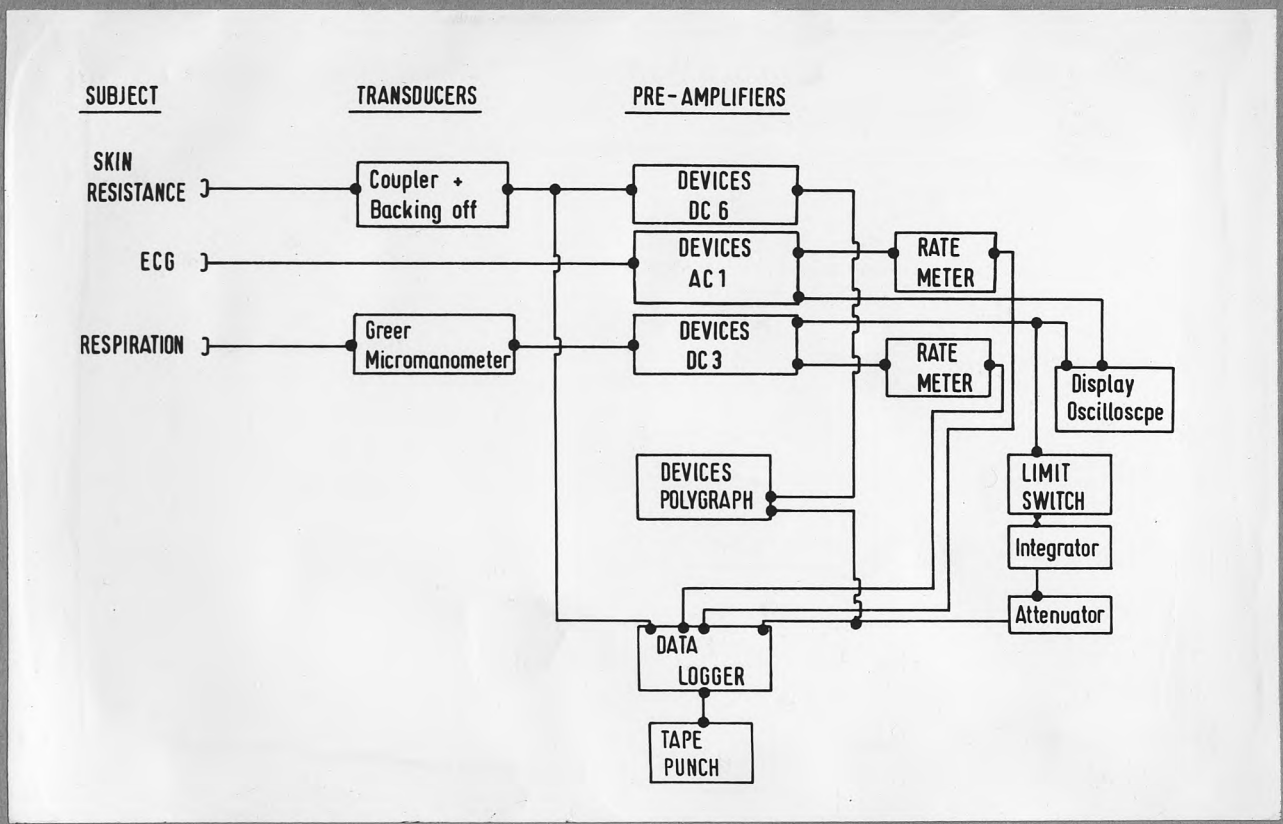


Fig. 2.1 Diagrammatical illustration of the arrangement, and the connection between, the instruments in the Psychophysiology Laboratory.
The circuit for measuring respiration, shown in diagram, was not used in this study.

3. The Experimental Procedure

The tests employed in this study were described in Chapter II (Part II) of this thesis. They can be divided into two broad categories :

I. The Physiological tests which consisted of

(A) The skin conductance measures :-

(i) skin conductance level;

(ii) frequency of spontaneous fluctuations in skin conductance;

(iii) magnitude of the psycho-galvanic reflex - P.G.R. - to a standard stimulus;

(iv) rate of habituation of the P.G.R.

(B) Heart Rate, H.R.

(C) Rate of resting fore-arm blood flow, F.B.F.

II. The psychometric tests which consisted of

(A) The Cornell Medical Index, C.M.I.

(B) Taylor's Manifest Anxiety Scale, T.M.A.S.

(C) Visual Analogue Scale, V.A.S.

At inception, before treatment began, each subject attended for the pre-treatment study at the Psychophysiology Laboratory. A tape-recorded account of the experimental procedure (see Appendix I ) was played back for the subject while sitting in the experimental cubicle. This was then followed, first, by the recording of the skin conductance measures, and the heart rate; and, second, by the measurement of the fore-arm blood flow.

When /

When the psychophysiological measurements had been completed, the subject then filled in the C.M.I. and the T.M.A.S., and was given the Visual Analogue Scale forms to take home to complete daily until the next laboratory visit.

These observations were again repeated at 12 weeks after treatment had been started.

(A) The Skin Conductance Measures. The technique used in the recording of these measures involved passing a current of constant magnitude, from an external direct current (D.C.) source, through two-element electrodes attached to the subject's skin. The resistance, and therefore the conductance, of the skin could then be measured. The principle underlying this method is illustrated in Fig. 2.2. A current of constant magnitude was passed from V through $R_1$ and the outer annulus $O_1$-$O_2$ of the active electrode. As a result, a voltage developed across the inner annulus $I_1$-$I_2$ of the electrode. This voltage was then backed off by $V_B$ so that a zero voltage was effected. Deviations from this value could then be measured via the D.C. amplifier and polygraph. By Ohm's Law, V = I.R.; since I was constant, V (voltage) was therefore proportional to the resistance, R. In order to obtain a current of constant strength, $R_1$ was chosen so that it was high relative to any possible value of $R_s$. For example, if V = 100V, and $R_1$ = 10 Mego hm, the current flowing in the circuit would be 9.99 microamps if $R_s$ = 10 K, and 9.75 microamps when $R_s$ = 250K. The variation was thus only 2.5%.

The Electrodes. The two element type of electrodes used were slight modifications of the type advocated by Lykken (1959).

They /

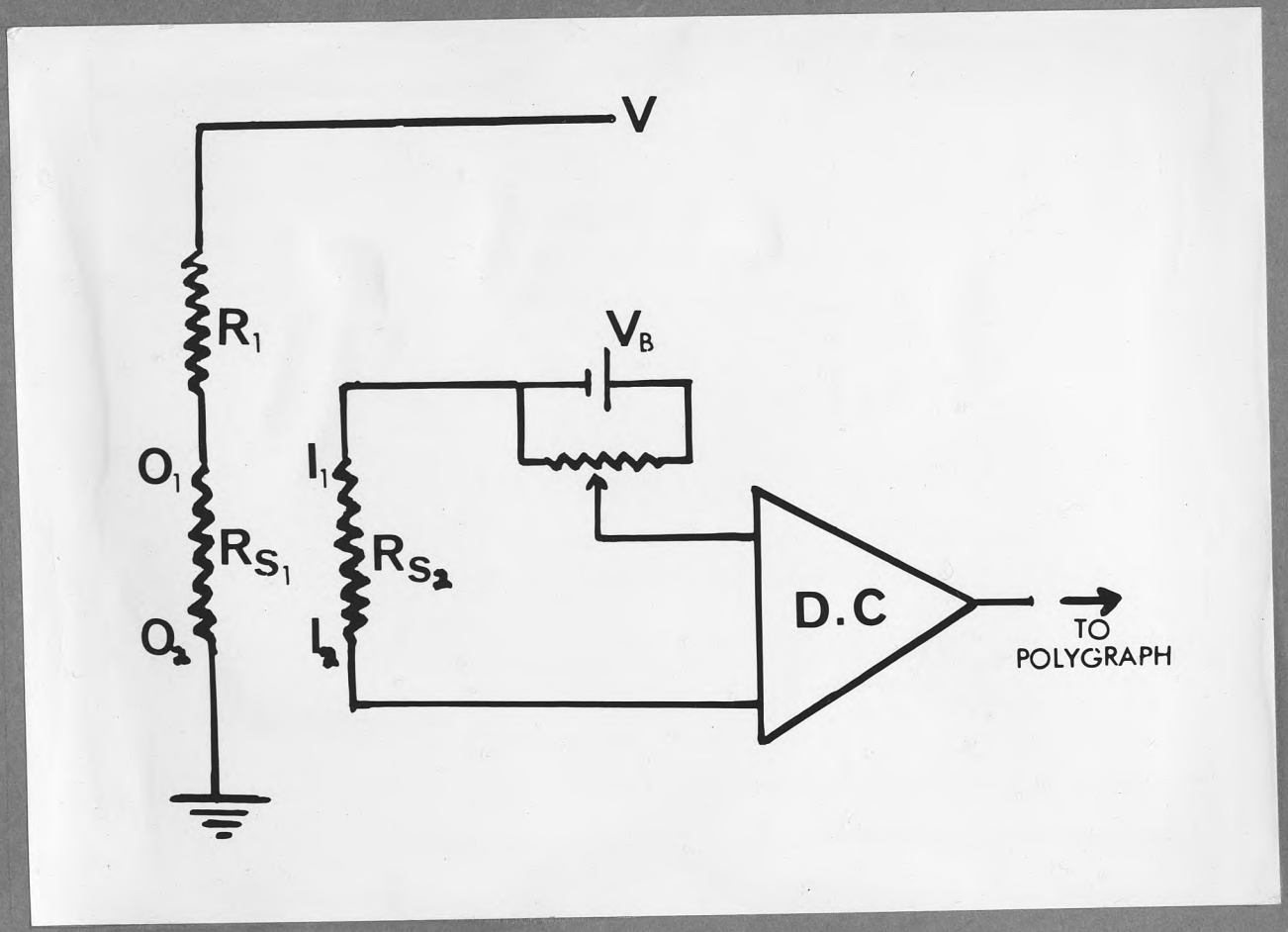


Fig. 2.2 Showing the theoretical circuit underlying the method of measuring the skin resistance (conductance), using a current of constant magnitude and two-element electrodes. Symbols are explained in the text.

They were made from lead, but the dimensions have been increased in accordance with the recommendations of Montagu (1963) so as to enable use with current size of 10 microamps. This gave a current density of 14 microamps per $cm^2$ at the active electrode.

The electrodes were scrubbed on an emery paper, followed by being thoroughly rinsed in running tap water, and dried with soft tissue paper just before being used in each experiment.

The Electrolyte used was the K=Y water soluble lubricating jelly (Johnson and Johnson).

Preparation of the Skin, and Placement of the Electrodes. The palmar surface of the distal phalanx of the thumb was chosen as the "active" site for electrode placement. According to Kuno (1956), this is the area of maximum density of sweat glands. The lateral surface of the arm, about 5 cm. distal to the lateral epicondyle of the humerus, was chosen as the site for the placement of the reference electrode.

The following steps were always taken in each experiment :-

a. The palmar surface of the subject's right thumb was wiped clean and dry with a piece of cotton wool,

b. A corn plaster pad ( Scholls ) was placed over the central whorl of the thumb and the electrode jelly applied generously. The pad limited the spread of the jelly.

c. Jelly was then applied generously to the "active" electrode, which was then centred on the corn pad and held lightly but firmly in position with P.C.V. adhesive tape.

d. /

d. The skin area for the "reference" electrode was treated differently. The aim in this case was to reduce the resistance of the area chosen to as low a minimum as possible. This was achieved either by scraping gently with the finer nail or rubbing the area fairly vigorously with cottonwool moistened with electrode jelly.

e. A generous amount of jelly was applied to the electrode which was then retained in position with P.V.C. adhesive tape.

When all electrodes had been placed and properly connected, the experimenter left the cubicle, and started the recording. The procedure followed in the recording was identical to the one described in detail by Lader and Wing (1966).

(B) Heart Rate. The measurement of heart rate was done simultaneously as the skin resistance. Heart rate is comparatively easier to record. The discrete nature of heart beats also makes it easier to handle statistically. The technique of recording used in this study is based on the principles of electrocardiography and cardiotachometry.*

Standard electrocardiograph (E.C.G.) bipolar leads were employed, lead I being used in almost all cases. Where it was difficult to get satisfactory wave form on lead I, lead II was used. This, however, was necessary on only two occasions.

Fig. 2.3 illustrates diagrammatically the lay-out of the Leads from the electrodes on the subject's wrists (standard lead I) which pass to the E.C.G. amplifier. Output from this amplifier could be displayed on an oscilloscope so that the E.C.G. wave form is available for inspection.

A /

* A cardiotachometer is an instrument which directly provides records of heart rate.

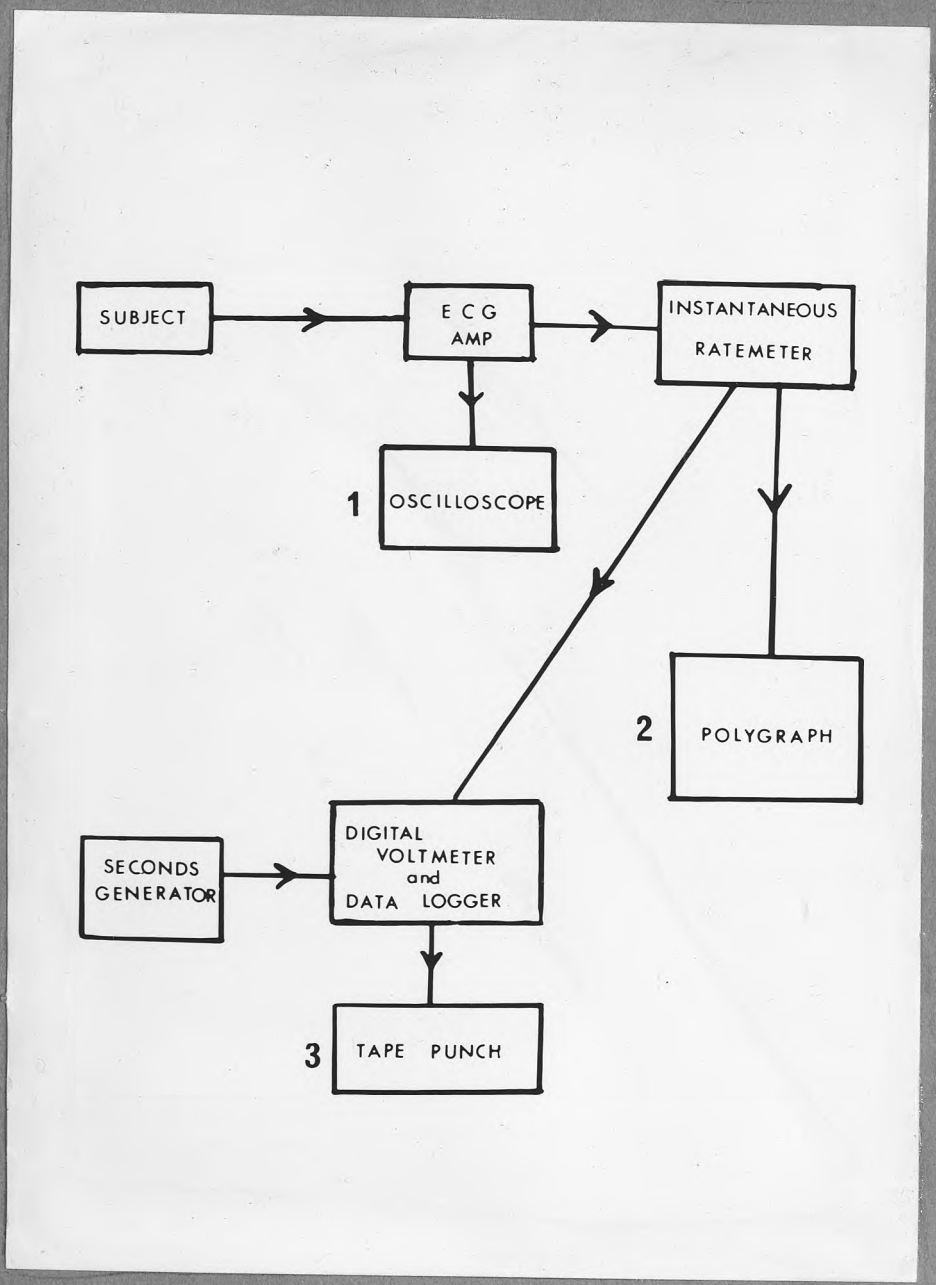


Fig. 2.3 Diagrammatical illustration of the heart rate recording.
Figure shows the three levels of observation, 1 to 3.

A second output passes to the cardiotachometer, an instantaneous rate meter (Devices) based on a circuit developed by Dr. J. Neilson of the Department of Medical Physics, University of Edinburgh. This instrument measures the interval between two heart beats, i.e. the interbeat interval (I.B.I.) and gives an output voltage, V, which is inversely proportional to I.B.I.; i.e. $f = \frac{1}{\text{I.B.I.}}$ where f = the heart rate per minute.

The output from the ratemeter was passed into a two-channel Devices M.R. Pen Recorder (Polygraph), and also to a Digital Voltmeter (Solatron). The latter was connected to a seconds generator which "commanded" it every 10 seconds to punch the heart rate on a paper tape in a form suitable for digital computer analysis. Thus there were three levels of observation :

(i) Inspection of the E.K.G. wave form on an oscilloscope.

(ii) Pen-recording of heart rate directly on paper.

(iii) Punching of the heart rate on a paper tape for computer analysis and storage purposes.

(C) Forearm Blood Flow. The technique used in the measurement of the forearm blood flow was that of venous occlusion plethyomography. (Barcroft 1953; Kelly 1967). This technique is based on the theoretical assumption that if the venous return from a part of a limb is prevented while the arterial flow into the limb is not restricted, the resultant increase in volume of the limb per unit time is the Blood flow.

Due to the all-involving nature of this experiment, it always had to be carried out separately from the skin conductance and heart rate measurements. The subject lay on a comfortable standard examination couch in the controlled laboratory environment.

The /

The subject's head was supported on a pillow and made as comfortable as possible. After dusting the left forearm with talcum powder, a loose but closely fitting through-and-through sleeve was slipped on to the forearm. This sleeve was made of thin latex rubber fixed to central holes (of given circumferences) in two 1/4in/thick rubber discs or diaphragms, one at each end. Various sizes of these sleeves were available in the laboratory, and each was chosen according to the circumferences of the subject's fore-arm taken 14 cm. apart. The arm, together with the sleeve was put into the plethysmograph shown in Fig. 2.4. Detachable semi-circular aluminimum plates were placed in position so that the diaphragms lay between the plates and the plethysomograph. The rubber discs or diaphragms were then firmly bolted to the 2-in. wide metal flange at each end of the plethysmograph by means of the nuts.

The plethysmograph was then filled with water at $39^{0}$C through the glass chimney while air was pumped out of the apparatus by continually squeezing a rubber bulb beneath it. The thermometer aperture was kept open to allow the air to escape. When the plethysmograph had been filled, the thermometer was put in position and more water was added until the water level was 2-3 cm. above the plimsole line. Gentle tilting of the plethysmograph after this helped to eliminate any remaining air.

Two pneumatic sphygmomanometer cuffs were then applied, one at the wrist, and the other on the arm proximal to the plethysmograph. Both could be inflated from large reservoirs of compressed air, the pressures of which were maintained by two foot pumps. During recording, pressure of 200 mm. Hg. was maintained at the wrist cuff to produce arterial occlusions, and 60-70 mm Hg. at the second cuff for venous return occlusion only.

Calibration /

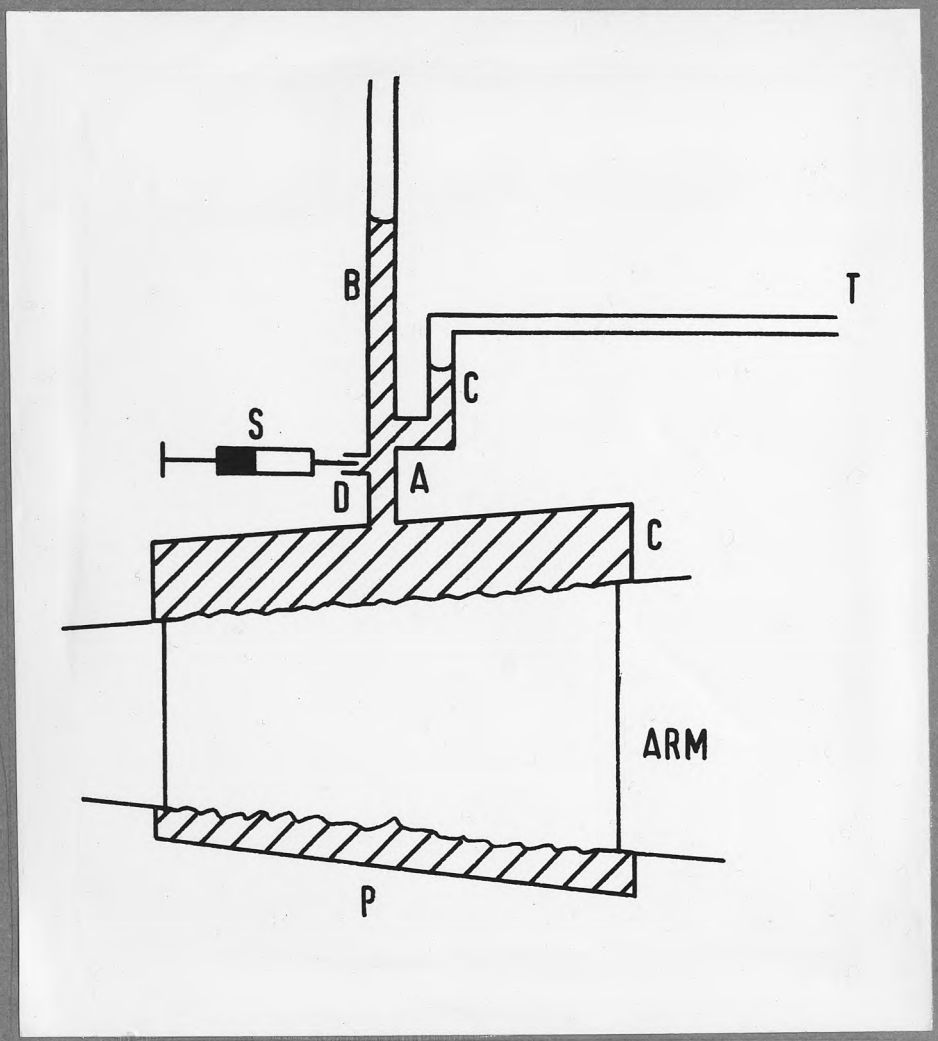


Fig. 2.4 A diagrammatical illustration of the venous occlusion plethysmograph with the forearm positioned, and the instrument water-filled. S, syringe; T, tube to manometer; B, glass chimney; A, side connection for tube, T; D, a two-way tap connecting syringe to glass chimney.

Calibration was done by fairly rapidly but steadily injecting 3 ml. of water from a syringe into the water-filled plethysmograph, and noting the magnitude of pen deflection in the recorder. Four calibration measurements were taken.

After calibration, the subject was encouraged to relax and engage in no activity whatsoever. The wrist cuff was inflated to 200 mm. Hg. and maintained at that pressure for one full minute before starting the pen recorder and also inflating the second cuff to 60-70 mm. Hg. The venous return from the forearm was thus occluded while the arterial inflow was unimpeded. The resultant increase in the volume of the forearm caused pressure changes in the plethysmograph which were transmitted to the pen recorder. After about 15-20 secs., the pressure in the venous occluding cuff was released and the blood which had accumulated in the forearm was allowed to return into the general circulation. The recording procedure was again repeated after an interval of 30-45 sec. This was continued until ten such intermittent measurements had been made.

At the end of ten recordings, the pressures in both cuffs was released and the calibration was repeated. The water in the plethysmograph was drained into a graduated glass jar, and its volume noted. This was deducted from the volume of the plethysmograph (1360 ml.) to give the volume of that part of the forearm which had been enclosed in it.

Calculation of forearm blood flow. Fig. 2.5 shows a typical tracing from a recording. The gradient of volume increase with time represents the blood flow. This is given by the formula :

$$\frac{d}{s} \times \tan \theta \times \frac{100}{V} \text{ ml/100 ml. vol. of arm/minute}$$

where /

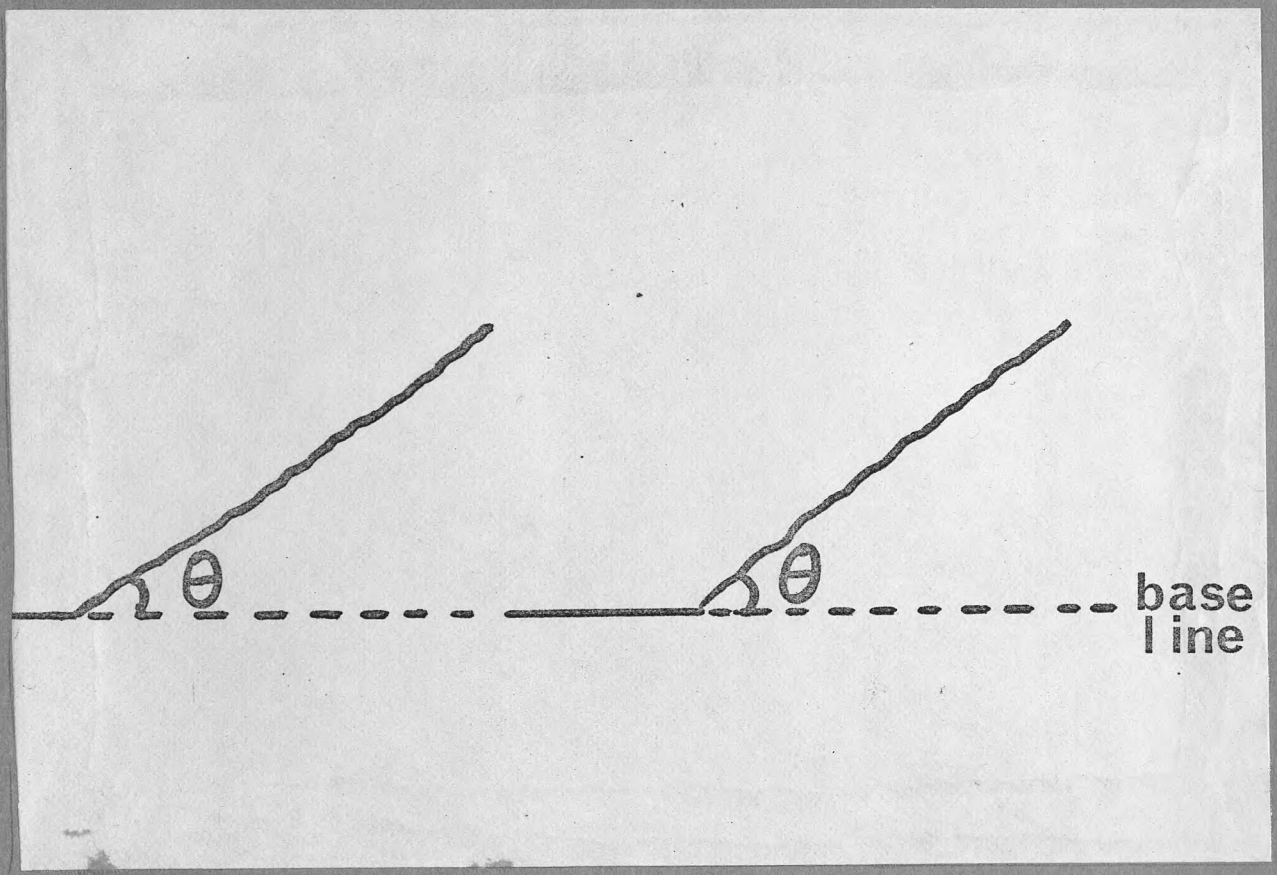


Fig. 2.5 Showing changes in the rate of forearm blood - upward going curve - during measurement by venous occlusion plethysmography.

where d = mean calibration pen deflection per ml. of water injected, s = spread of pen recorder in cm. per minute. Tan $\theta$ the gradient of the slope of the tracing, and V = volume of arm in ml.

4. Statistical Considerations.

In most of the calculations in this study, the usual parametric statistical tests were employed. These included Student's t test, Linear Regressions, Pearson's coefficient of product-moment correlation, Fisher's Analysis of Variance and of Covariance (Snedecor 1956).

In order to assess the effect of treatment more easily with an analysis of variance, the hyperthyroid group of 20 patients was sub-divided into two groups of 10 patients each. Each of these groups was therefore comparable in size with the two comparison groups of 10 subjects per group. There were therefore :

(a) two diagnostic categories (hyperthyroid v. comparison group)

(b) four groups (2 hyperthyroid groups v. treated comparison group v. untreated comparison)

designated as "Diagnosis" and "Groups" respectively in the Tables of Analysis of Variance.

Where applicable the Chi-Square ($\chi^2$) Test has been used. In some grossly skewed distributions, e.g. Variability in levels of Self-Rated Anxiety on an Analogue Scale, it was necessary to apply a non-parametric test. In the example cited, the Mann-Whitney U-Test was employed. The results obtained with this test were also counter-checked with the Median Test.

In /

In calculating variability, the conventional statistic - the variance - has not been used. Instead a time-series statistic, which takes into consideration the time-ordered nature of the data and their changing mean level, was used. This was the Mean Square Successive Difference (M.S.S.D. or $d^2$), developed by von Neumann (1941). The convential variance ($s^2$) measures the dispersion of a series of data independently of the order of the observation of such data. It therefore excludes the effect of trend. Whereas the variance ($s^2$) is given by :

$$s^2 = \frac{\sum_{i=1}^{n} (x_i - \bar{x})}{n}$$

the M.S.S.D. ($d^2$) is computed as

$$d^2 = \frac{\sum_{i=1}^{n-1} (x_{i+1} - x_i)^2}{n - 1}$$

where $\bar{x}$ is the mean value of a series of observations, x; n is the total number of observations; and the subscript, i, refers to the temporal order of the observations. The M.S.S.D. makes use of all the n - 1 available successive differences. The first difference, $d_1$ is equal to $x_2 - x_1$; and the second difference, $d_2$ is equal to $x_3 - x_2$; they are related in that they both involve $x_2$.

Leiderman /

Leiderman and Shapiro (1962) have illustrated the advantages of this statistic in psychological and physiological experiments. They drew attention to the immense potential value of a statistic of this type in the study of continuously changing physiological and psychological processes. The ratio $d^2/_{s^2}$ is called the von Neumann Ratio (VNR) and may be used to test for randomness or trend in a time-series. It bears a linear relationship to the serial correlation (R) between $x_i$ and $x_i + 1$. When n is large, it can be shown that V.N.R. is approximately equal to 2 (1 - R). Thus the lower the V.N.R., the greater the time-ordered trend. Von Neumann et al (1941) gives the efficiency of $d^2$ in estimating the standard deviation as

$$\frac{2\,(n-1)}{3n-4} \quad \doteq \quad \frac{2}{3}\quad\left(1+\frac{1}{3n-4}\right)$$

The efficiency is unity for n = 2, and approaches a limiting value of 2/3 as n becomes very large.

To demonstrate the superiority of $d^2$ in estimating the variability of a time-ordered observation, three patterns of the levels of anxiety (rated daily by some of the subjects in this study) are shown in Fig. 2.6. The mean $(\bar{x})$, variance $(s^2)$, and the M.S.S.D. $(d^2)$ have been computed for each subject's self-ratings. The mean and the variance are approximately equal for the three curves. It would be easily noted, however, that the uppermost curve appears to be more variable than the middle one which is in turn more variable than the curve at the bottom. These differences are borne out by $d^2$.

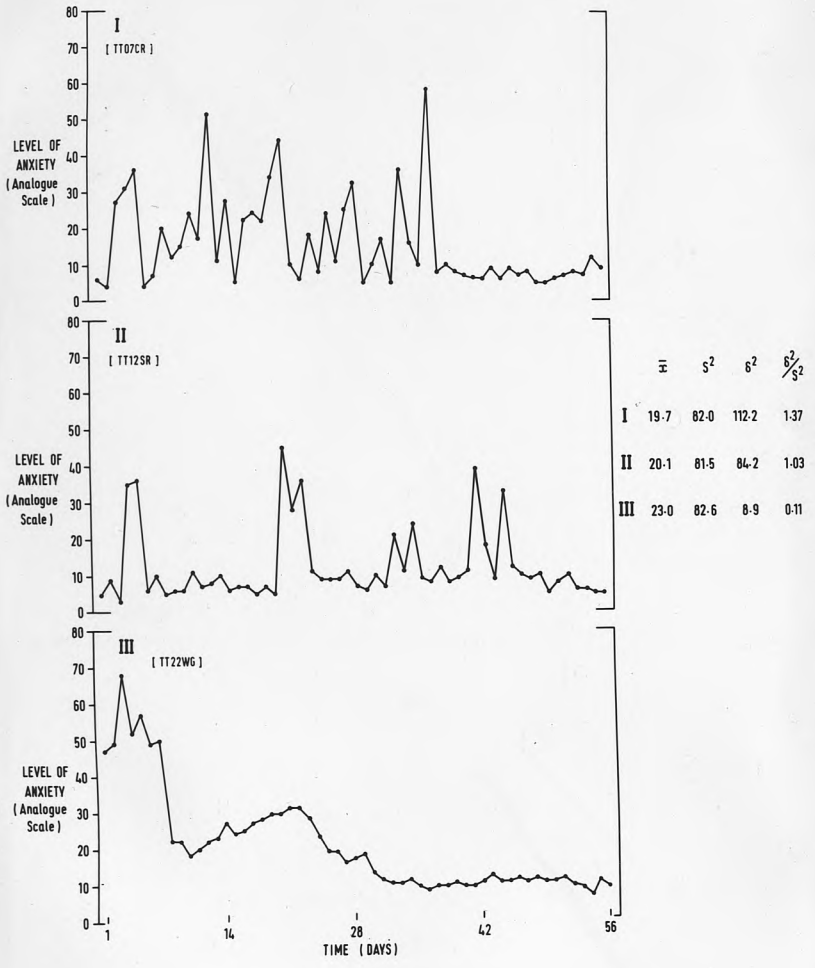


Fig. 2.6 Showing the comparison between two measures of variability - the variance, $s^2$, and the mean square successive differences, $d^2$. Ratings by individual patients on the Visual Analogue Scale have been used to plot the graphs shown.

# CHAPTER IV

## RESULTS

1. Skin Conductance Level (SCL)

Pre-Treatment. Fig. 3.1 shows the pre-treatment mean skin conductance levels for the hyperthyroid and comparison subjects over the 32-minute period of a PGR habituation experiment. The points on the graph are each an average of 4 readings taken at minute intervals in accordance with the method of Lader and Wing (1966). The curve is divided into two parts: the resting period covering the first 12 minutes of the experiment, and the remaining 20 minutes during which the subject was repeatedly presented with a 1000Hz tone - 100dB loudness intensity of 1 second duration, at random intervals varying between 45 and 85 seconds.

Lader and Wing (op. cit.) found that, in normal subjects, the SCL showed little increase during the resting period. With the first tone presentation, it rose sharply and continued to increase slowly until about the latter part of the second period when it began to fall. By the end of the experiment, it had shown an appreciable fall but was still higher than the level for the first 4 minutes of the experiment. The hyperthyroid and the comparison subjects in this study showed a steady rise in their mean SCL's from the beginning to the end of the experiment. The hyperthyroid group had a higher mean SCL than the comparison group. Such patterns of increase as these, over a fairly long period, have been described as tonic arousal.

The /

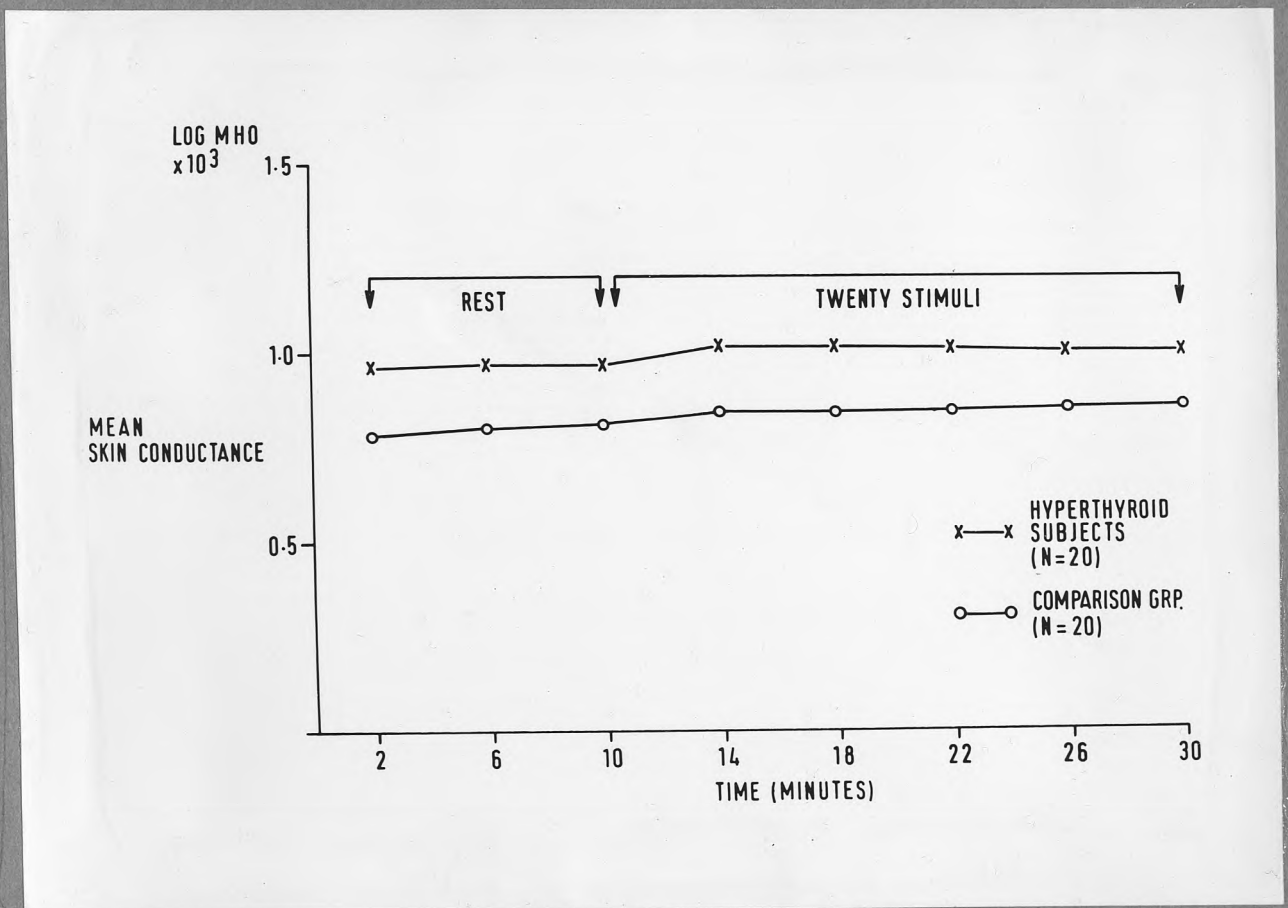


Fig. 3.1 The effect of 20 auditory stimuli on the pre-treatment skin conductance level.

The subjects of this study showed no evidence of a fall in skin conductance level. In Table 3.1, the mean skin conductance levels during the first 10 minutes of the resting period are compared. It can be seen that the hyperthyroid subjects had a higher conductance level ($P<0.05$), indicating a higher palmar sweat gland activity.

The Effect of Treatment. Fig 3.2. shows the changes in the post-treatment SCLs under an experimental situation identical to that for Fig 3.1. There has been an appreciable fall in the mean SCL of the hyperthyroid subjects for the entire period of the experiment. The treated comparison group also have a lower mean SCL than their untreated counterparts. The pattern of change in the SCLs was, however, not different from the pre-treatment pattern.

2. Spontaneous Fluctuations in Skin Conductance

Pre-Treatment. Fig. 3.3 shows the pre-treatment mean spontaneous fluctuations (frequency/minute) for the hyperthyroid and comparison subjects over the 32-minute period of a P.G.R. habituation experiment. The 32 readings were divided into 8 groups with 4 in each group. The average value for each group was used in plotting the curves in the Figure. The hyperthyroid subjects show a definite decrease in the number of spontaneous fluctuations as the experiment proceeded, while the comparison group remained at more or less the same level of frequency of spontaneous fluctuations.

The /

| | Hyperthyroid Group N = 20 | | Comparison Group N = 20 | | Normals[+] N = 22 | | Significance of Differences * | | |
|---|---|---|---|---|---|---|---|---|---|
| | Mean | s.d. | Mean | s.d. | Mean | s.d. | Hyperthyroid Group v. Comparison Group | Hyperthyroid Group v. Normal | Comparison Group v. Normal |
| Mean Skin Conductance Level (log mho $\times 10^{3}$) | 957.8 | 232.5 | 794.8 | 239.2 | 817.7 | 188.8 | $P < 0.05$ | $P < 0.002$ | P = N.S. |

*t test

[+]Rosenthal (Unpublished)

Table 3.1 Showing the pre-treatment skin conductance levels. The value quoted for the group of normal (healthy) subjects was obtained in the same laboratory where the present study was done.

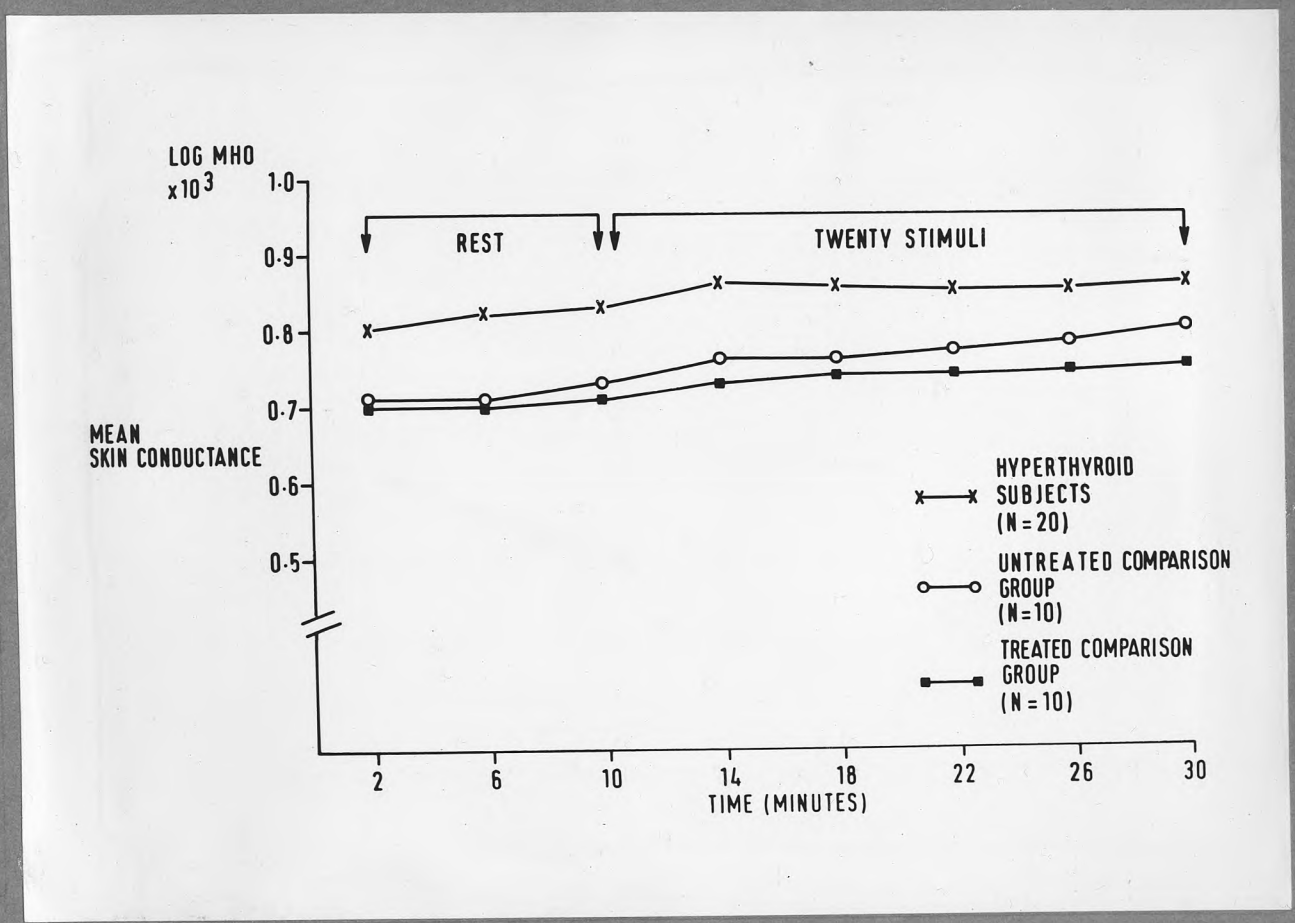


Fig. 3.2 The effect of 20 auditory stimuli on the post-treatment skin conductance level.

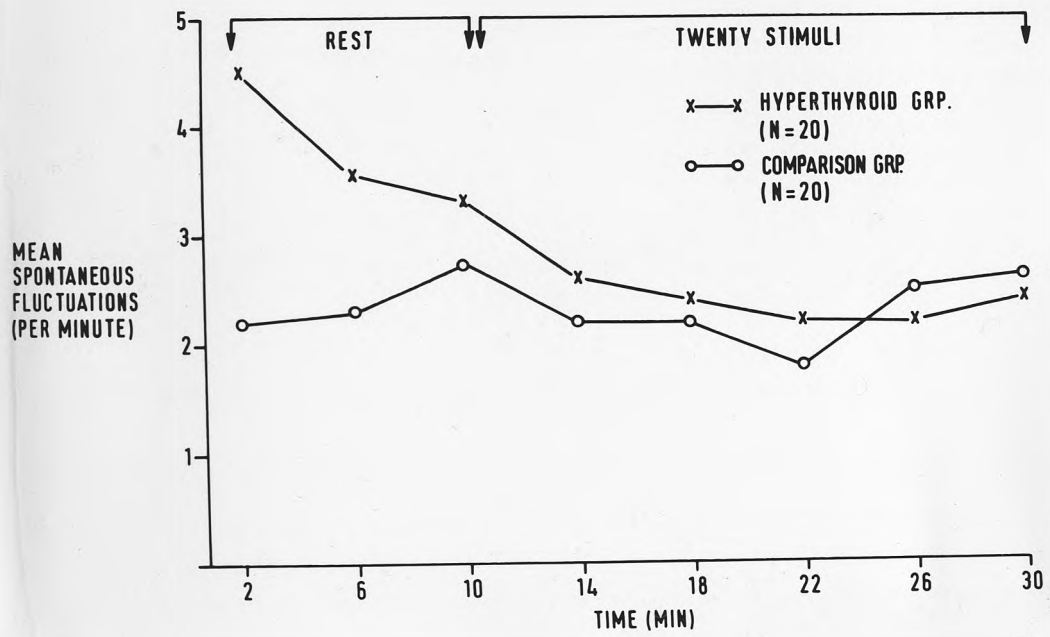


Fig. 3.3 Showing the effect of 20 auditory stimuli on the pre-treatment spontaneous fluctuations in skin conductance.
Only fluctuations > = 0.003 log micro mhos were regarded as significant and counted.

The frequency of the resting spontaneous fluctuation was determined by calculating the mean frequency/minute over the first 10 minute period of the experiment. Table 3.2 shows the mean resting spontaneous fluctuations for the hyperthyroid and comparison groups. The difference between the mean values for the hyperthyroid group, and the comparison group was significant ("t" = 2.25; d.f. = 38; $P < 0.05$).

The Effect of Treatment. This is shown in Fig. 3.4 The interaction between the groups and treatment was examined by an analysis of variance (Table 3.3). Though there was a very highly significant difference between the pre-treatment and post-treatment values combined for all the groups, ($F = 14.45$; d.f. = 1/38; $P < 0.001$), this was accounted for mainly by the hyperthyroid subjects; they showed a highly significant difference in their trend towards a lower rate of spontaneous fluctuations, when compared with the two comparison groups ($F = 6.30$; d.f. = 1/36; $P < 0.025$).

Fig. 3.5 shows the pattern of spontaneous fluctuations changes during the post-treatment habituation experiment. There seems to be very little difference between the changes in the three groups of subjects. The hyperthyroid group showed a generally much lower rate of spontaneous fluctuations than they did before treatment was started. No significant difference could be detected between the first four-minute period and any other four-minute period of the experiment

3. Magnitude of Psycho-galvanic Reflex (P.G.R.)

Pre-Treatment /

| | Hyperthyroid Group N = 20 | | Comparison Group N = 20 | | Normals + N = 22 | | Significance of Differences * | | |
|---|---|---|---|---|---|---|---|---|---|
| | Mean | s.d. | Mean | s.d. | Mean | s.d. | Hyperthyroid Group v. Comparison Group | Hyperthyroid Group v. Normal | Comparison Group v. Normal |
| Rating Spontaneous Fluctuations (Frequency/ min.) | 3.8 | 2.5 | 2.2 | 2.0 | 1.9 | 1.4 | $P < 0.05$ | $P < 0.05$ | P = N.S. |

+Rosenthal (Unpublished) *t test

Table 3.2 Showing the pre-treatment spontaneous fluctuations in skin conductance during a resting period of 10 minutes. The value quoted for the 'normals' was obtained in the same laboratory where the present study was done.

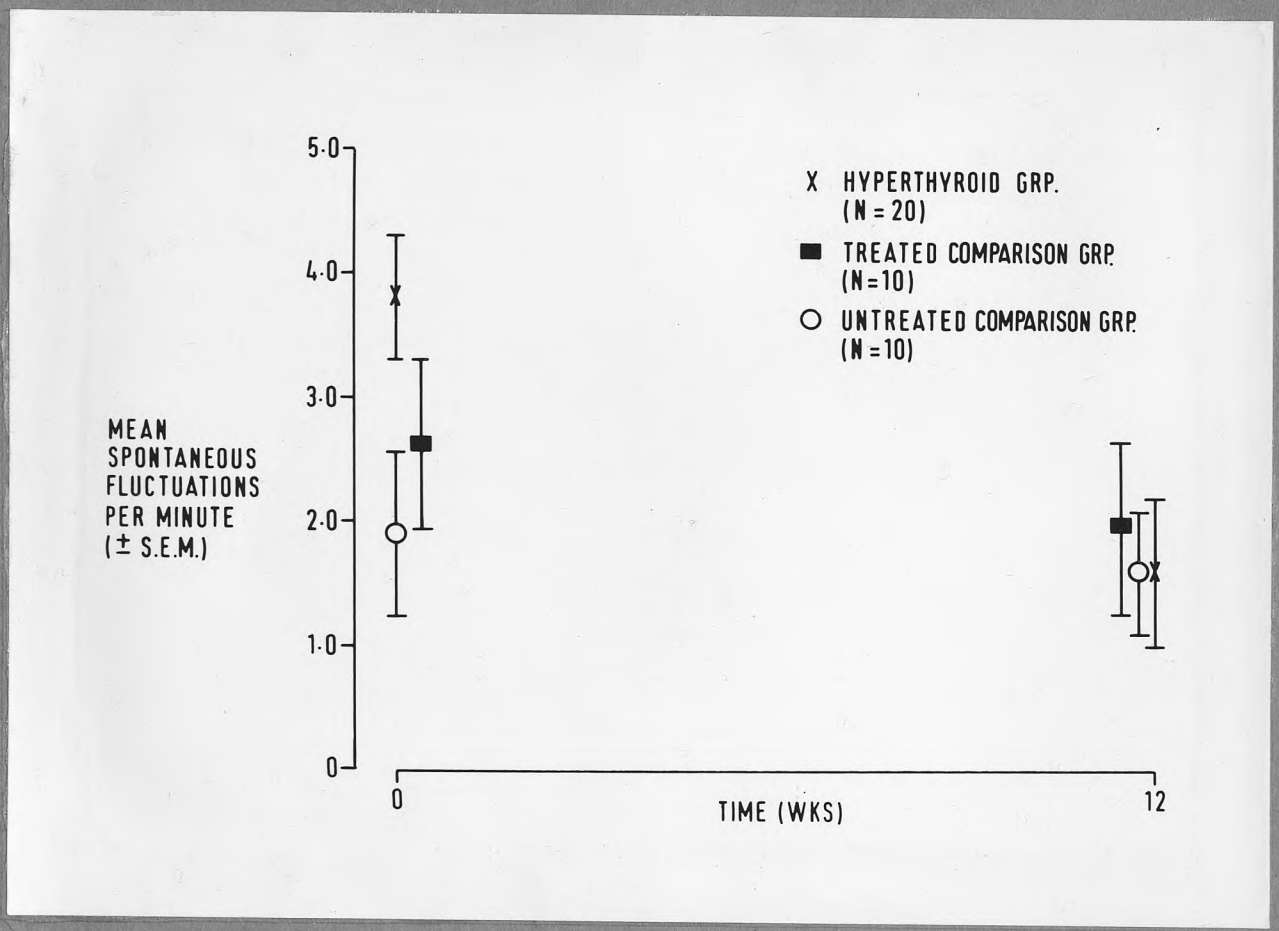


Fig. 3.4 The effect of treatment on the spontaneous fluctuations in skin conductance during a ten-minute resting period. Only fluctuations > = 0.003 log micro mho were regarded as significant.

| Source of Variation | Sums of Squares | d.f. | Mean Square | F | P |
|---|---|---|---|---|---|
| 1. Diagnosis | 9.1125 | 1 | 9.1125 | 1.46 | N.S. |
| 2. Group | 0.3125 | 1 | 0.3125 | 0.05 | N.S. |
| 3. Group X Diagnosis | 9.1125 | 1 | 9.1125 | 1.46 | N.S. |
| 4. Error | 225.4500 | 36 | 6.2625 | | |
| 5. Treatment | 35.1125 | 1 | 35.1125 | 14.45 | <0.001 |
| 6. Diagnosis X Treatment | 15.3125 | 1 | 15.3125 | 6.30 | <0.025 |
| 7. Group X Treatment | 0.0125 | 1 | 0.0125 | 0.005 | N.S. |
| 8. Group X Diagnosis X Treatment | 0.6125 | 1 | 0.6125 | 0.25 | N.S. |
| 9. Error | 87.4500 | 36 | 2.4292 | | |
| 10. Total | 382.4875 | 79 | | | |

Table 3.3 Table of Analysis of Variance of the effect of treatment on the resting spontaneous fluctuations (frequency/min) of hyperthyroid and comparison subjects.

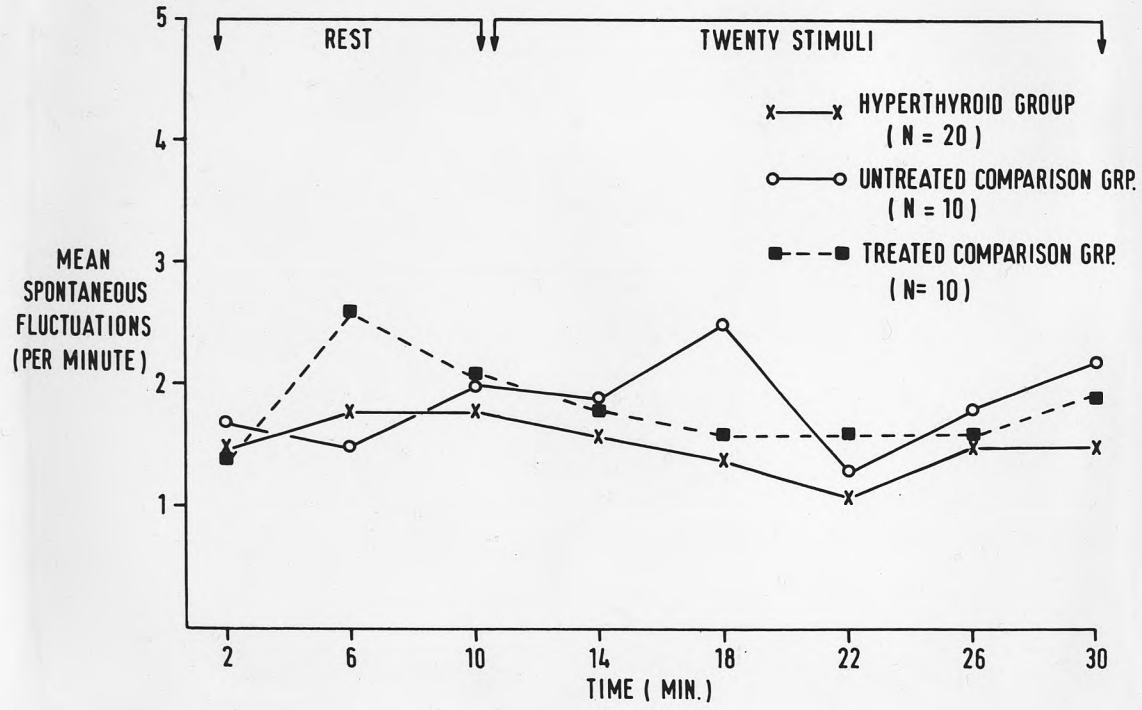


Fig. 3.5 Showing the effect of 20 auditory stimuli on the post-treatment spontaneous fluctuations in skin conductance.
Only fluctuations > = 0.003 log micro mho were regarded as significant and counted.

Pre-Treatment. This was assessed by calculating the mean of the three biggest reflexes, excluding the first one, elicited in the subject during the course of the habituation experiment. Hyperthyroid subjects showed a much greater responsivity than the comparison subjects ("t" = 2.76; d.f. = 38; $P < 0.01$). This is shown in Table 3.4. It will be seen that the mean response in the hyperthyroid group was more than twice that in the comparison group. The mean response elicited by the twentieth stimulus in the hyperthyroid subjects was equivalent to that of the fifth stimulus in the comparison group. (Fig. 3.7).

Effect of Treatment. This is shown in Fig. 3.6 and Table 3.5. The interaction between the groups with respect to treatment was examined by an analysis of variance (Table 3.6). The diminution in magnitude of the P.G.R. in hyperthyroid subjects to less than half the pre-treatment value was confirmed beyond the 1 per cent level of significance. The treated comparison group have shown a similar but less striking dimunition in their responsivity, while the untreated comparison group showed a much less appreciable decrease.

4. Habituation of the Psycho-Galvanic Reflex (P.G.R.)

1. Pre-Treatment. When the rate of habituation of the subjects was assessed individually by regression analysis, only five (25 per cent) of the hyperthyroid subjects failed to reach the significant level for habituation. In comparison, nine (45 per cent) of the comparison subjects failed to habituate. A chi-square estimation of difference showed that there was no significant difference between the two groups ($X^2 = 0.99$; d.f. = 1; P = N.S.)

Both /

| | Hyperthyroid Group N = 20 | | Comparison Group N = 20 | | Significance of Difference * |
|---|---|---|---|---|---|
| | Mean | s.d. | Mean | s.d. | |
| Magnitude of psycho-galvanic reflex | 55.0 | 44.5 | 24.6 | 21.3 | $P < 0.01$ |

*t test

Table 3.4 Showing the pre-treatment magnitudes of the psycho-galvanic reflex (change in log mho x $10^3$) to a standard stimulus of 1000 Hz tone at 100dB lasting one second.

| | Pre - Treatment | | Post - Treatment | |
|---|---|---|---|---|
| | Mean | s.d. | Mean | s.d. |
| Hyperthyroid Group N = 20 | 55.0 | 44.5 | 20.5 | 18.3 |
| Treated Comparison Group N = 10 | 21.9 | 25.0 | 12.5 | 7.5 |
| Untreated Comparison Group N = 10 | 27.4 | 17.7 | 21.9 | 33.1 |

Table 3.5 The effect of treatment on the magnitude of psycho-galvanic reflex, given as change in log mho x $10^3$, to a standard stimulus of 1000 Hz tone at 100dB lasting 1 second.

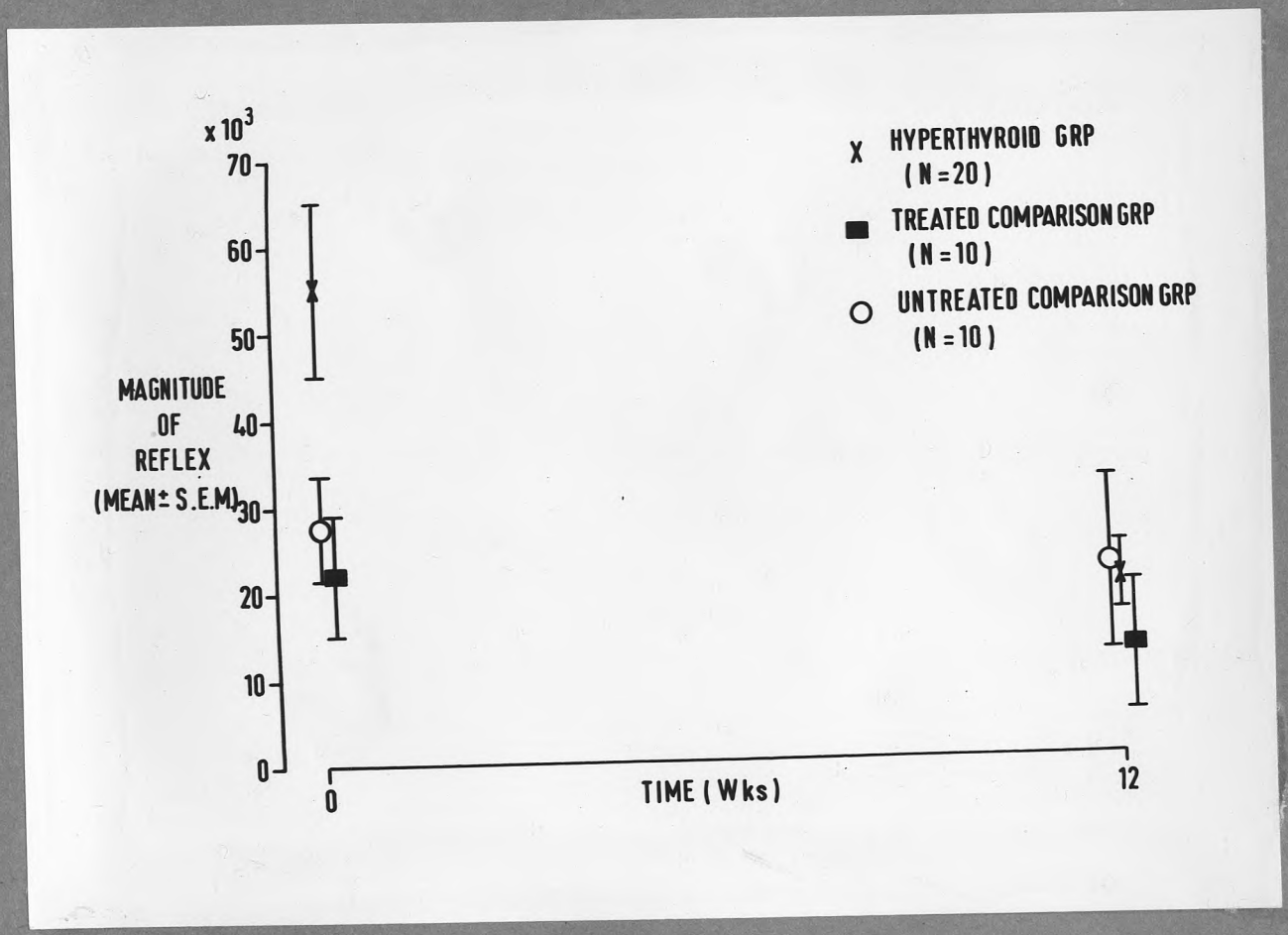


Fig. 3.6 The effect of treatment on the magnitude of the psycho-galvanic reflex. The vertical bars represent the standard error of the mean (S.E.M.).

| Source of Variation | Sum of Squares | d.f. | Mean Square | F | P |
|---|---|---|---|---|---|
| 1. Diagnosis | 0.005638 | 1 | 0.005638 | 7.73 | <0.01 |
| 2. Group | 0.000307 | 1 | 0.000307 | 0.42 | N.S. |
| 3. Group X Diagnosis | 0.000248 | 1 | 0.000248 | 0.34 | N.S. |
| 4. Error | 0.026259 | 36 | 0.000729 | | |
| 5. Treatment | 0.008795 | 1 | 0.008795 | 8.66 | <0.01 |
| 6. Diagnosis X Treatment | 0.003648 | 1 | 0.003648 | 3.59 | <0.1 |
| 7. Group X Treatment | 0.000099 | 1 | 0.000099 | 0.10 | N.S. |
| 8. Group X Diagnosis X Treatment | 0.000002 | 1 | 0.000002 | 0.002 | N.S. |
| 9. Error | 0.036575 | 36 | 0.001016 | | |
| 10. Total | 0.081571 | 79 | | | |

Table 3.6 Table of Analysis of Variance of the effect of treatment on the magnitude of psychogalvanic reflex.of Hyperthyroid and Comparison Subjects.

Both groups are compared with samples of healthy persons and people with specific phobias in Table 3.7.

Fig. 3.7 shows the curves for the regression of the mean psychogalvanic reflexes of the hyperthyroid and comparison subjects. It shows that, on the whole, both groups of subjects habituated beyond the 0.1% level of significance. The table of analysis of covariance, Table 3.8, however, shows that the rate of habituation by the hyperthyroid subjects was much higher than that for the comparison subjects ($F = 34.00$; d.f. = 1/34; $P < 0.001$). Though not entirely so, this finding appears to be in accordance with the different numbers of individuals failing to habituate in each group. Lader (1964) found that there was a high negative correlation (-0.90) between the slope (b-value) of regression curve and the origin of the curve on the Y-axis (a-value). A correlation of -0.93 was found in this study. This dependence of the b-value on the a-value introduced an obstacle when comparing individuals or groups. In order to overcome this, Lader (op. cit.) proposed a formula for calculating a slope (b'-value) which would be independent of the a-value. He called this absolute value the habituation score, H-score, computed from the formula,

$$b' = b - c\,(a - \bar{a})$$

where $b'$ = the H-score, b= slope of the regression curve for each individual, a = the respective a-value, c = the slope of the regression curve of the b-values on the a-values in the population under consideration, and $\bar{a}$ = the mean value of all the a-values. When the H-scores were computed, the hyperthyroid subjects were found to have a lower mean value, -0.0103 (s.d. = 0.0195), than the comparison subjects -0.0163 (s.d. = 0.0069).

This /

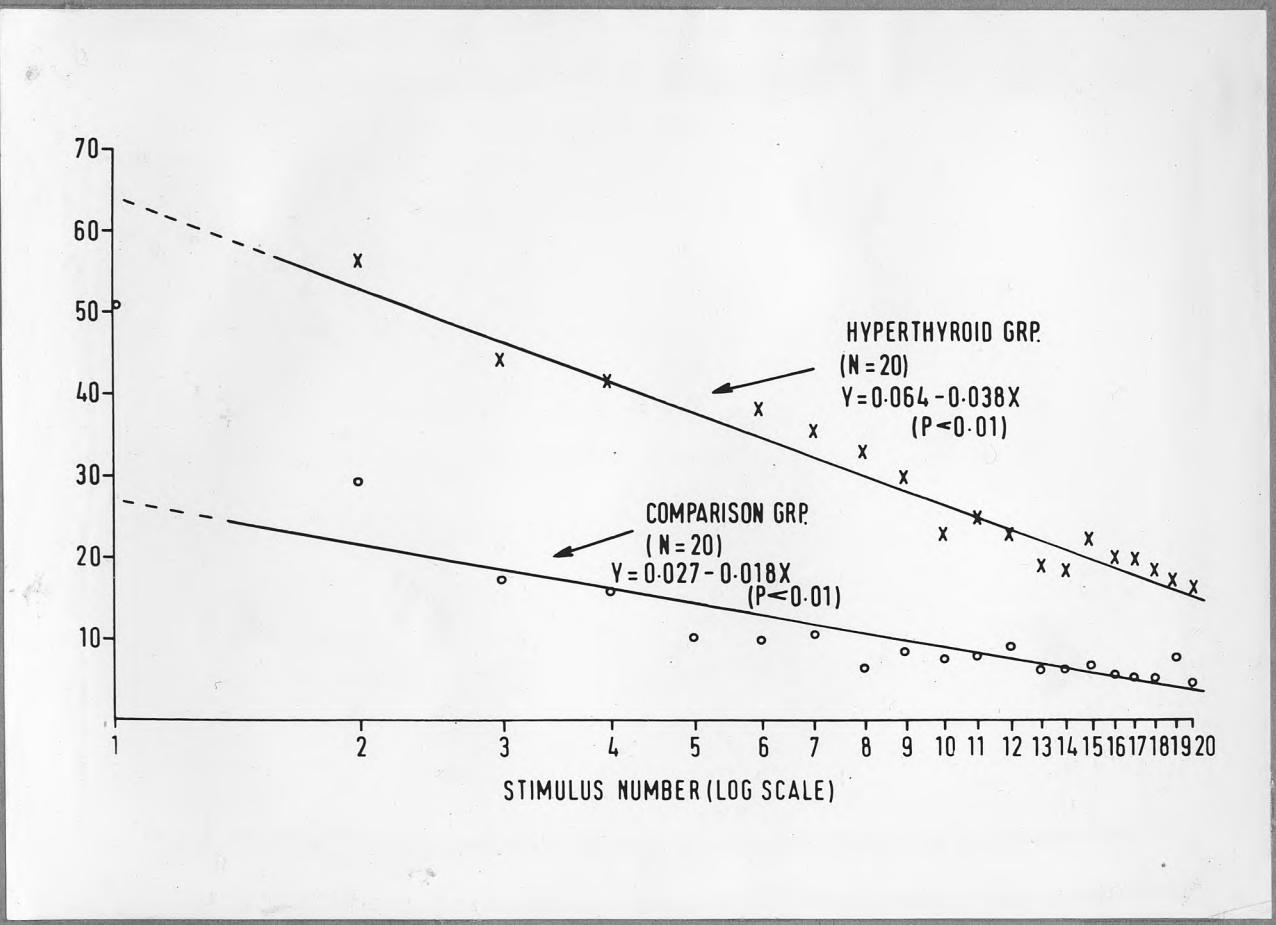


Fig. 3.7 Showing the regression curves of the pre-treatment mean psycho-galvanic reflexes on the log stimulus number. The magnitude of the reflex (change in log mho x $10^3$) is given on the Y - axis.

| | Hyperthyroid Subjects N = 20 | Comparison Subjects N = 20 | Sample of Healthy Population* N = 75 | Specific Phobics*+ N = 14 N = 19* |
|---|---|---|---|---|
| Percentage habituating at $P < 0.05$ | 75 % | 55 % | 85 % | 64 - 76 % |

* Lader (1967) ; + Daly, Aitken and Rosenthal (1970)

Table 3.7 Habituation of the Psycho-galvanic Reflex to a repeated standard stimulus.

| Source | Deviation from Regression | Degrees of Freedom | Mean Square | F | P |
|---|---|---|---|---|---|
| 1. Hyperthyroid Group | 0.000153 | 17 | 0.000009 | | |
| 2. Comparison Group | 0.000122 | 17 | 0.000007 | | |
| 3. Within | 0 .000275 | 34 | 0.000008 | | |
| 4. Regression Coefficient | 0.000272 | 1 | 0.000272 | 34.00 | <0.001 |
| 5. Common | 0.000547 | 35 | 0.000015 | | |

Table 3.8 Table of Analysis of Covariance of the pre-treatment P.G.R. habituation curves.

This put the hyperthyroid group more towards the neurotic end than the comparison group. The much smaller standard deviation for the comparison group would indicate that this group was more homogeneous than the hyperthyroid. The difference in the variances was significant ($F = 7.99$; d.f. = 19/19; $P = 0.001$).

The Effect of Treatment. Fig. 3.8 shows the trends of the mean habituation scores, for the various groups, after treatment. The trend in the hyperthyroid group was towards an improvement. In the comparison group under treatment, it was more or less static while the trend was towards a deterioration in the comparison group without treatment. The interaction between the groups and treatment was examined by an analysis of variance (Table 3.9). The differences in the trends of the habituation scores of the various groups were not statistically significant.

Fig. 3.9 shows the regression curves for the mean psycho-galvanic reflexes of the various groups after 12 weeks of treatment. Only the comparison subjects not on treatment failed to reach the 5 per cent level of significance. An analysis of covariance shows no difference between the hyperthyroid and the treated comparison group (Table 3.10).

5. Forearm Blood Flow (F.B.F.)

Pre-Treatment. The pre-treatment mean resting forearm blood flow for the hyperthyroid subjects was 3.8 ml. of blood per 100 ml. of forearm per minute (s.d. = 1.9). The comparison subjects had a lower value of 2.1 ml. of blood per 100 ml. of forearm per minute (s.d. = 1.2); the difference between the mean values was highly significant ("t" = 3.38; d.f. = 38; $P < 0.002$).

Both /

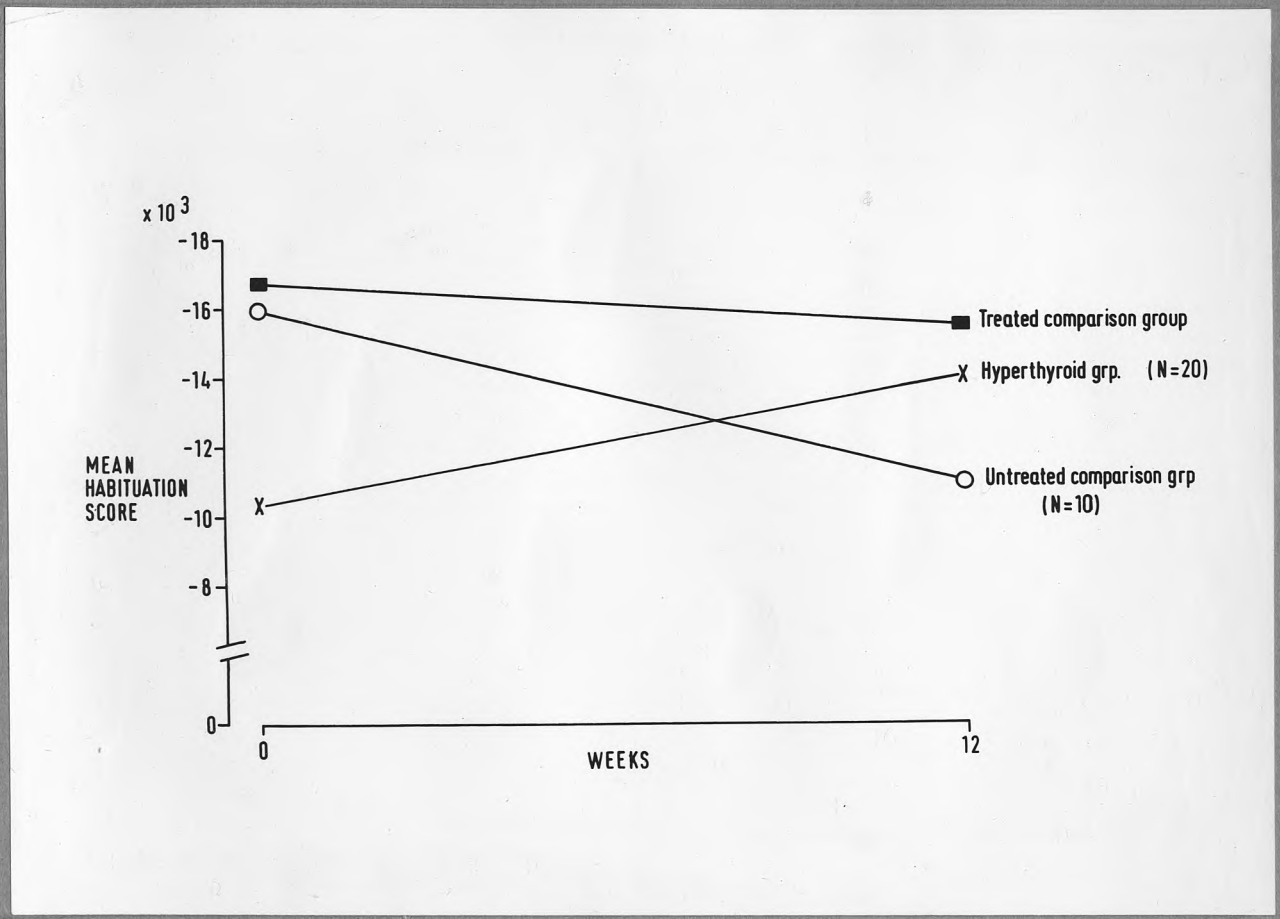


Fig. 3.8 Showing the effect of treatment on the habituation scores.

| Source of Variation | Sums of Squares | d.f. | Mean Square | F | P |
|---|---|---|---|---|---|
| 1. Diagnosis | 0.0001869 | 1 | 0.0001869 | 1.12 | N.S. |
| 2. Group | 0.00000001 | 1 | 0.00000001 | 0.00 | N.S. |
| 3. Group X Diagnosis | 0.0001402 | 1 | 0.0001402 | 0.84 | N.S. |
| 4. Error | 0.00600625 | 36 | 0.0001668 | | |
| 5. Treatment | 0.00000067 | 1 | 0.00000067 | 0.01 | N.S. |
| 6. Diagnosis X Treatment | 0.0001697 | 1 | 0.0001697 | 1.25 | N.S. |
| 7. Group X Treatment | 0.0000510 | 1 | 0.0000510 | 0.38 | N.S. |
| 8. Group X Diagnosis X Treatment | 0.0000014 | 1 | 0.0000014 | 0.01 | N.S. |
| 9. Error | 0.0048735 | 36 | 0.0001354 | | |
| 10. Total | 0.0114297 | 79 | | | |

Table 3.9 Table of Analysis of Variance of the effect of treatment on the Habituation Scores of the Hyperthyroid and Comparison Subjects.

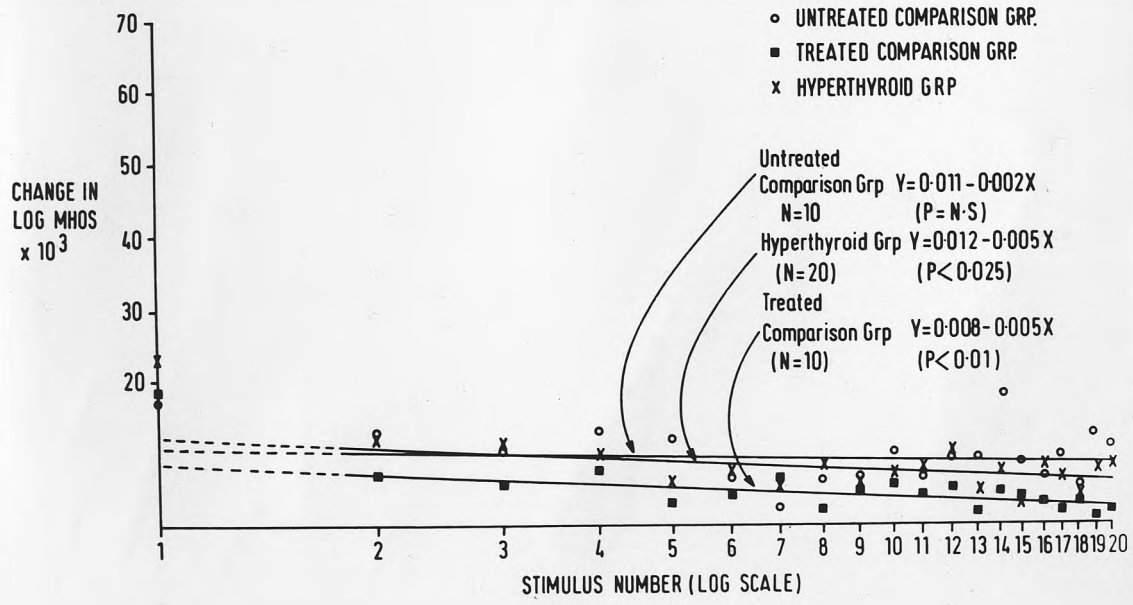


Fig. 3.9 Showing the regression curves of the post-treatment mean psycho-galvanic reflexes on the log stimulus number.

| Source | Deviation from Regression | Degrees of Freedom | Mean Square | F | P |
|---|---|---|---|---|---|
| 1. Hyperthyroid Group | 0.000066 | 17 | 0.0000038 | | |
| 2. Comparison Group | 0.000037 | 17 | 0.0000021 | | |
| 3. Within | 0.000103 | 34 | 0.0000030 | | |
| 4. Regression Coefficient | 0.0000006 | 1 | 0.0000006 | 0.2 | N.S. |
| 5. Common | 0.0001024 | 35 | 0.0000029 | | |

Table 3.10 Table of Analysis of Covariance of the post-treatment P.G.R. habituation curves for the hyperthyroid group, and the comparison group on psychotropic drugs. See Fig. 3.9.

Both values were compared with the mean value for a population of healthy subjects and two relevant diagnostic groups in Table 3.11.

The Effect of Treatment. This is shown in Fig. 3.10 and Table 3.12. The interaction between the groups and treatment was examined by an analysis of variance, Table 3.13. The difference between the pre-treatment values, combined for all groups, was very highly significant ($F = 15.92$; d.f. = 1/36; $P < 0.001$). This was due mainly to the hyperthyroid subjects who had a larger difference in their pre- and post-treatment values in contrast with the two comparison groups combined ($F = 10.99$; d.f. = 1/36; $P < 0.001$). The treated comparison group had a larger but statistically insignificant difference than the untreated comparison group ($F = 3.45$; d.f. = 1/36; $0.1 > P > 0.05$).

6. Heart Rate (H.R.)

Pre-Treatment. The mean resting heart rate for the hyperthyroid subjects was 112.1 per minute (s.d. = 16.2); and for the comparison subjects, it was 90.4 per minute (s.d. = 13.1). The difference between these values was very highly significant ("t" = 4.66; d.f. = 38; $P < 0.001$).

The Effect of Treatment. Fig 3.11 shows the trend of the heart rate with treatment. The two comparison groups showed no significant change while the fall in heart rate of the hyperthyroid subjects was very highly significant ("t" = 5.0; d.f. = 38; $P < 0.001$).

| | Hyperthyroid Group N = 20 | Comparison Group N = 20 | Normals* N = 60 | Chronic Anxiety* N = 45 | Specific+ Phobics N = 14 |
|---|---|---|---|---|---|
| Mean and Standard Deviations | 3.8 ± 1.9 | 2.1 ± 1.2 | 2.2 ± 1.0 | 4.4 ± 1.3 | 2.4 ± 1.5 |

* Kelly and Walter (1969); + Daly, Aitken, and Rosenthal (1970)

t test significant differences between various groups:

| | P < |
|---|---|
| Hyperthyroid v. Normal ..... | 0.001 |
| Hyperthyroid v. Comparison Group ..... | 0.002 |
| Hyperthyroid v. Chronic Anxiety ..... | N.S. |
| Hyperthyroid v. Specific phobias ..... | 0.05 |
| Comparison Group v. Normal ..... | N.S. |
| Comparison Group v. Chronic Anxiety ..... | 0.001 |
| Comparison Group v. Specific phobias ..... | N.S. |

Table 3.11 Showing the mean resting fore-arm blood flow (± standard deviation) for hyperthyroid and comparison subjects, and the published mean values for various groups.

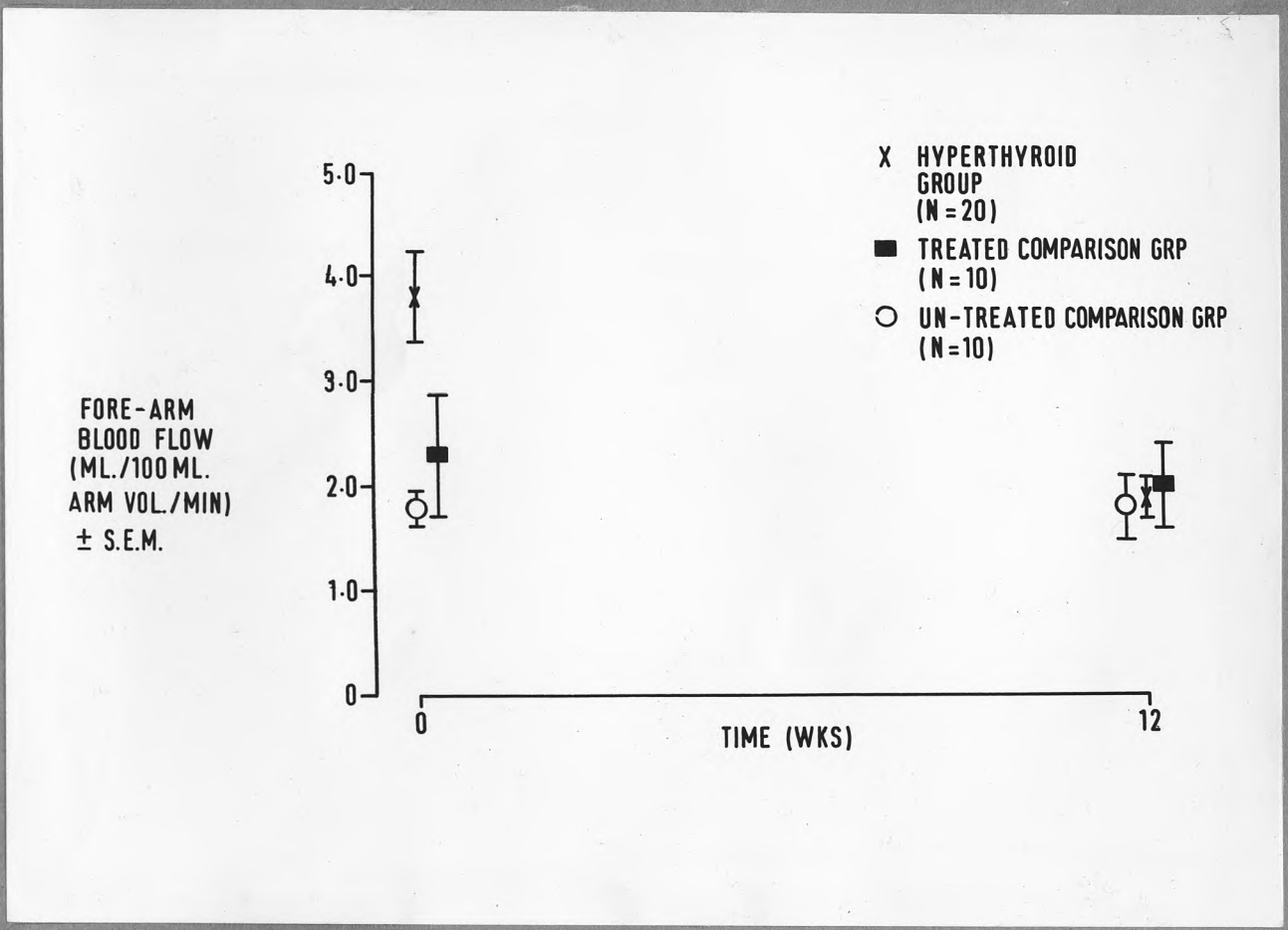


Fig. 3.10 Showing the effect of treatment on the forearm blood flow. Mean values were used in plotting the graph; the vertical bars represent the standard error of the mean (S.E.M.)

| Group | N | Pre-Treatment | | Post-Treatment | |
|---|---|---|---|---|---|
| | | Mean | s.d. | Mean | s.d. |
| Hyperthyroid Group | 20 | 3.8 | 1.9 | 1.9 | 0.9 |
| Treated Comparison Group | 10 | 2.3 | 1.7 | 2.0 | 1.3 |
| Untreated Comparison Group | 10 | 1.8 | 0.5 | 1.8 | 0.9 |

Table 3.12 Showing the effect of treatment on the resting forearm blood flow. (ml. per 100ml. volume of arm per minute)

| | Source of Variation | Sums of Squares | d.f. | Mean Square | F | P |
|---|---|---|---|---|---|---|
| 1. | Diagnosis | 15.14 | 1 | 15.14 | 8.86 | <0.01 |
| 2. | Group | 0.97 | 1 | 0.97 | 0.57 | N.S. |
| 3. | Group X Diagnosis | 6.27 | 1 | 6.27 | 3.67 | <0.1 |
| 4. | Error | 61.53 | 36 | 1.71 | | |
| 5. | Treatment | 22.68 | 1 | 22.68 | 15.92 | <0.001 |
| 6. | Diagnosis X Treatment | 15.66 | 1 | 15.66 | 10.99 | <0.01 |
| 7. | Group X Treatment | 4.90 | 1 | 4.90 | 3.45 | <0.1 |
| 8. | Group X Diagnosis X Treatment | 9.11 | 1 | 9.11 | 6.39 | <0.025 |
| 9. | Error | 51.30 | 36 | 1.42 | | |
| 10. | Total | 187.57 | 79 | | | |

Table 3.13 Table of Analysis of Variance of the effect of Treatment on the Forearm Blood Flow of Hyperthyroid and Comparison Subjects.

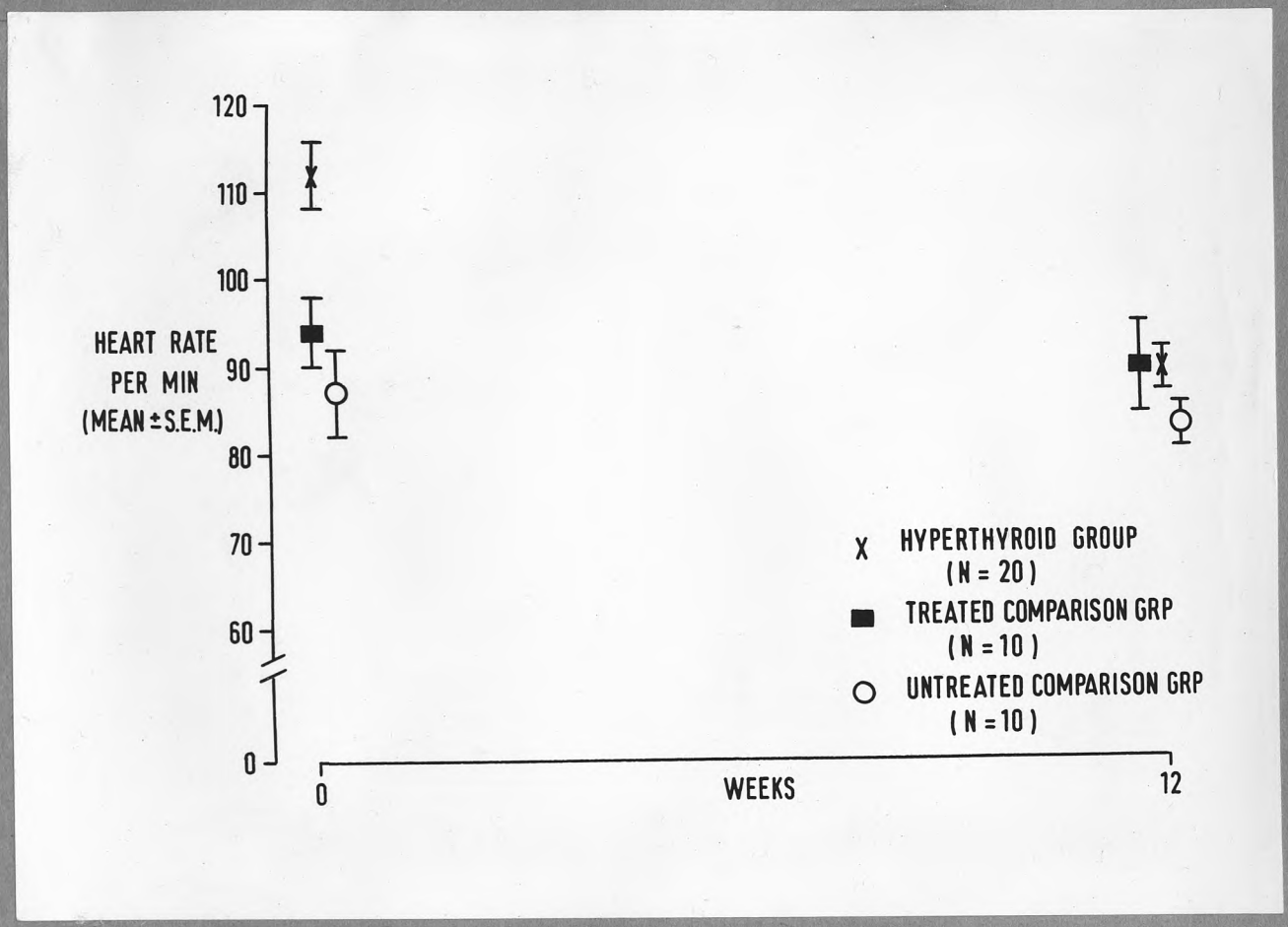


Fig. 3.11 Showing the effect of treatment on the heart rate. The vertical bars represent the standard error of the mean (S.E.M.)

7. The Cornell Medical Index.

Pre-Treatment. Scores on this index, as in most previous studies, were used in this study as an assessment of the degree of psychiatric morbidity and patterns of feelings. A score of 30 on the entire questionnaire, or 10 on the M - R scale, was taken as indicative of significant psychiatric morbidity. On this basis, 12 patients (60 per cent) in the hyperthyroid group and 14 patients (70 per cent) in the comparison group were identified as having a significant degree of psychiatric morbidity. The difference between these proportions was not significant ($\chi^2 = 0.44$; d.f. = 1; P = N.S.)

The 50th percentile of the total score for the hyperthyroid group was at 42.5 (range 7-92) and of the M - R scale score, 7 (range 0-38). In comparison, the 50th percentile of the total score for the comparison group was 31.0 (range 12-60), and of the M - R scale score, 13.0 (range 2-32). Thus while the hyperthyroid subjects had a higher median on the total score, they seemed to have a lower median on the M - R scale. The M - R scale of the index contains only psychological questions as opposed to scale A - L which consists mainly of questions relating to symptoms or illnesses of somatic nature. It could be expected therefore that hyperthyroid subjects would show a higher score on the total scale since they would probably answer questions on the A - L scale more frequently in the affirmative.

A crude attempt was made to study in more detail the pattern of answers for the hyperthyroid as well as the comparison subjects. Six questions (1, 24, 36, 74, 140, 174) were identified which 50 per cent or more of one group answered in the affirmative as compared with 25 per cent

or /

or less of the other group. Of these six questions, all the four (1, 24, 36, 74) in favour of the hyperthyroid group were from the A - L sections of the index. Only three of these questions could be considered to be of specific relevance to hyperthyroidism, one (36) of which can be explained exclusively on somatic pathology. The two remaining questions in favour of the comparison group consisted of one each from sections A - L and M - R. These questions are listed in the Table below.

| | |
|---|---|
| 1. | Do you need glasses to read ? |
| 24. | Do you sometimes have severe soaking sweats at night ? |
| 36. | Are your ankles often badly swollen ? |
| 74. | Does your face often get badly flushed ? |
| 140 | Do you find it impossible to take a regular rest period each day ? |
| 174. | Are your feelings easily hurt ? |

Table 3.14 Showing those questions on the Cornell Medical Index which appear to have been differentially answered in the affirmative by hyperthyroid and comparison subjects.
The appended numbers refer to actual numbers of the questions in the index.

It /

It would seem therefore that the higher score by the hyperthyroid subjects on the total (A - R) scale might in part be accounted for by the positive answers in response to questions, relating to the somatic aspects of their illness. However, the paucity of such questions, that are readily identifiable would suggest a somewhat small contribution from this quarter. The mean scores for the two groups on the total and M - R scales showed no significant differences from each other. See Table 3.15 and 3.16.

The Effect of Treatment. This is shown in Table 3.17. Using an analysis of variance, Table 3.18, it was observed that the combined post-treatment scores were highly significantly lower than the combined pre-treatment scores ($F = 11.71$; d.f. = 1/36; $P < 0.001$). But the pattern of change was similar in all the three groups and each group considered separately showed no statistical significance for the change in the mean score.

8. The Taylor Manifest Anxiety Scale (T.M.A.S.)

Pre-Treatment. Hyperthyroid subjects had a significantly higher mean score than normal (healthy) subjects ($P < 0.01$). This is shown in Table 3.19. It can be seen that hyperthyroids did not differ in their mean score from the comparison subjects, who in their turn showed a mean very highly significantly above the normals ($P < 0.001$). A score of 14 was used as the cut-off point above which the amount of anxiety could be regarded as abnormally high. On this basis, 14 (70 per cent) of the hyperthyroid subjects, and 16 (80 per cent) of the comparison subjects, were classified as having an abnormally high

| Scale | Hyperthyroid Group N = 20 | | Comparison Group N = 20 | | Significance of |
|---|---|---|---|---|---|
| | Mean | s.d. | Mean | s.d. | Differences* |
| Total | 42.3 | 24.5 | 34.0 | 15.9 | P = N.S. |
| M-R | 12.1 | 10.4 | 14.4 | 9.3 | P = N.S. |

*t test

Table 3.15 Showing the mean scores ($\pm$ s.d.) on Cornell Medical Index.

| Scale | Hyperthyroid Group N = 20 | | Comparison Group N = 20 | | Significance of |
|---|---|---|---|---|---|
| | Mean | s.d. | Mean | s.d. | Differences* |
| M: Inadequacy | 2.80 | 3.07 | 3.65 | 2.23 | P = N.S. |
| N: Depression | 0.95 | 1.76 | 0.40 | 0.82 | P = N.S. |
| O: Anxiety | 1.75 | 1.83 | 1.80 | 1.64 | P = N.S. |
| P: Sensitivity | 1.30 | 2.13 | 2.00 | 1.72 | P = N.S. |
| Q: Anger | 1.65 | 2.11 | 2.60 | 2.28 | P = N.S. |
| R: Tension | 3.60 | 2.30 | 3.95 | 2.78 | P = N.S. |

*t test

Table 3.16 Showing the break-down of the scores on the M-R scale of the C.M.I.

| Scale | Group | N | Pre-Treatment | | Post-Treatment | |
|---|---|---|---|---|---|---|
| | | | Mean | s.d. | Mean | s.d. |
| TOTAL | Hyperthyroid Group | 20 | 42.3 | 24.5 | 33.1 | 29.6 |
| | Treated Comparison Group | 10 | 33.5 | 16.3 | 27.9 | 20.3 |
| | Untreated Comparison Group | 10 | 34.4 | 16.3 | 28.5 | 17.2 |
| M-R | Hyperthyroid Group | 20 | 12.1 | 10.4 | 9.2 | 12.0 |
| | Treated Comparison Group | 10 | 15.7 | 10.8 | 11.7 | 12.1 |
| | Untreated Comparison Group | 10 | 13.1 | 8.0 | 8.8 | 7.2 |

Table 3.17 The effect of treatment on Cornell Medical Index Scores.

| | Source of Variation | Sums of Squares | d.f. | Mean Square | F | P |
|---|---|---|---|---|---|---|
| 1. | Diagnosis | 877.813 | 1 | 877.813 | 0.96 | N.S. |
| 2. | Group | 1776.613 | 1 | 1776.613 | 1.94 | N.S. |
| 3. | Group X Diagnosis | 1505.113 | 1 | 1505.113 | 1.64 | N.S. |
| 4. | Error | 33023.950 | 36 | 917.332 | | |
| 5. | Treatment | 1102.613 | 1 | 1102.613 | 11.71 | P < 0.001 |
| 6. | Diagnosis X Treatment | 56.113 | 1 | 56.113 | 0.60 | N.S. |
| 7. | Group X Treatment | 52.813 | 1 | 52.813 | 0.56 | N.S. |
| 8. | Group X Diagnosis X Treatment | 63.013 | 1 | 63.013 | 0.67 | N.S. |
| 9. | Error | 3390.95 | 36 | 94.193 | | |
| 10. | Total | 41848.99 | 79 | | | |

Table 3.18 Table of Analysis of Variance of the effect of Treatment on the C.M.I. (Total) Scores of Hyperthyroid and Comparison Subjects.

| Scale | Hyperthyroid Group N = 20 Mean | s.d. | Comparison Group N = 20 Mean | s.d. | Normals* N = 60 Mean | s.d. | Significance of Differences+ Hyperthyroid Group v. Comparison Group | Hyperthyroid Group v. Normal | Comparison Group v. Normal |
|---|---|---|---|---|---|---|---|---|---|
| Total | 21.1 | 11.2 | 21.8 | 9.1 | 14.0 | 7.9 | N.S. | $P < 0.01$ | $P < 0.001$ |

+t test *Kelly and Walter (1969)

Table 3.19 Showing the mean scores (and standard deviations) on the Taylor Manifest Anxiety Scale.

level of anxiety. The difference between these proportions was not significant ($\chi^2$ = 0.53; d.f. = 1; P = N.S.). The fiftieth percentiles for the hyperthyroid and comparison groups were 21, and 23 respectively (c.f. Taylor's figure of 13 for her sample of 1,971 normal, or healthy, subjects). The medians for the groups under consideration in this thesis put both groups at just beyond the eightieth percentile of Taylor's sample of healthy subjects.

The Effect of Treatment. As with the other psychometric tests used, there was a tendency for the mean scores of the various groups to drop by the end of 12 weeks. See Table 3.20. This trend was not statistically significant when each of the groups was considered on its own; but the combined means showed a very highly significant drop between the pre- and post-treatment scores (f = 20.3; d.f. = 1/36; P < 0.001). Examination of the interaction of the groups in producing this drop showed that the hyperthyroid group contributed more to the drop than the treated comparison group who in turn contributed more than their untreated counterparts, Table 3.21. However, the differences in contribution were not statistically significant. These trends are illustrated with Fig. 3.12 in which the median scores were used rather than the means. The median score for the hyperthyroid subjects, post-treatment, was 10.5 (c.f. Taylor's finding of 13 for normals). In contrast, the median scores for the treated and untreated comparison groups were 16.5 and 16.0 respectively.

It /

| Scale | Group | N | Pre-Treatment | | Post-Treatment | |
|---|---|---|---|---|---|---|
| | | | Mean | s.d. | Mean | s.d. |
| Total | Hyperthyroid Group | 20 | 21.1 | 11.2 | 15.6 | 12.9 |
| | Treated Comparison Group | 10 | 23.5 | 9.5 | 18.5 | 11.8 |
| | Untreated Comparison Group | 10 | 20.0 | 8.8 | 15.7 | 7.2 |

Table 3.20 The effect of treatment on the mean scores (and standard deviations) on the Taylor Manifest Anxiety Scale.

| | Source of Variation | Mean Square | d.f. | F | P |
|---|---|---|---|---|---|
| 1. | Diagnosis | 23.11 | 1 | 0.11 | N.S. |
| 2. | Group | 0.01 | 1 | 0.01 | N.S. |
| 3. | Group X Diagnosis | 201.61 | 1 | 0.95 | N.S. |
| 4. | Error | 211.94 | 36 | | |
| 5. | Treatment | 515.11 | 1 | 20.25 | <0.001 |
| 6. | Diagnosis X Treatment | 3.61 | 1 | 0.14 | N.S. |
| 7. | Group X Treatment | 78.01 | 1 | 3.07 | 0.1>P>0.05 |
| 8. | Group X Diagnosis X Treatment | 52.81 | 1 | 2.08 | N.S. |
| 9. | Error | 25.44 | 36 | | |
| 10. | Total | 119.24 | 79 | | |

Table 3.21 Table of Analysis of Variance of the effect of treatment on the T.M.A.S. scores of Hyperthyroid and Comparison Groups.

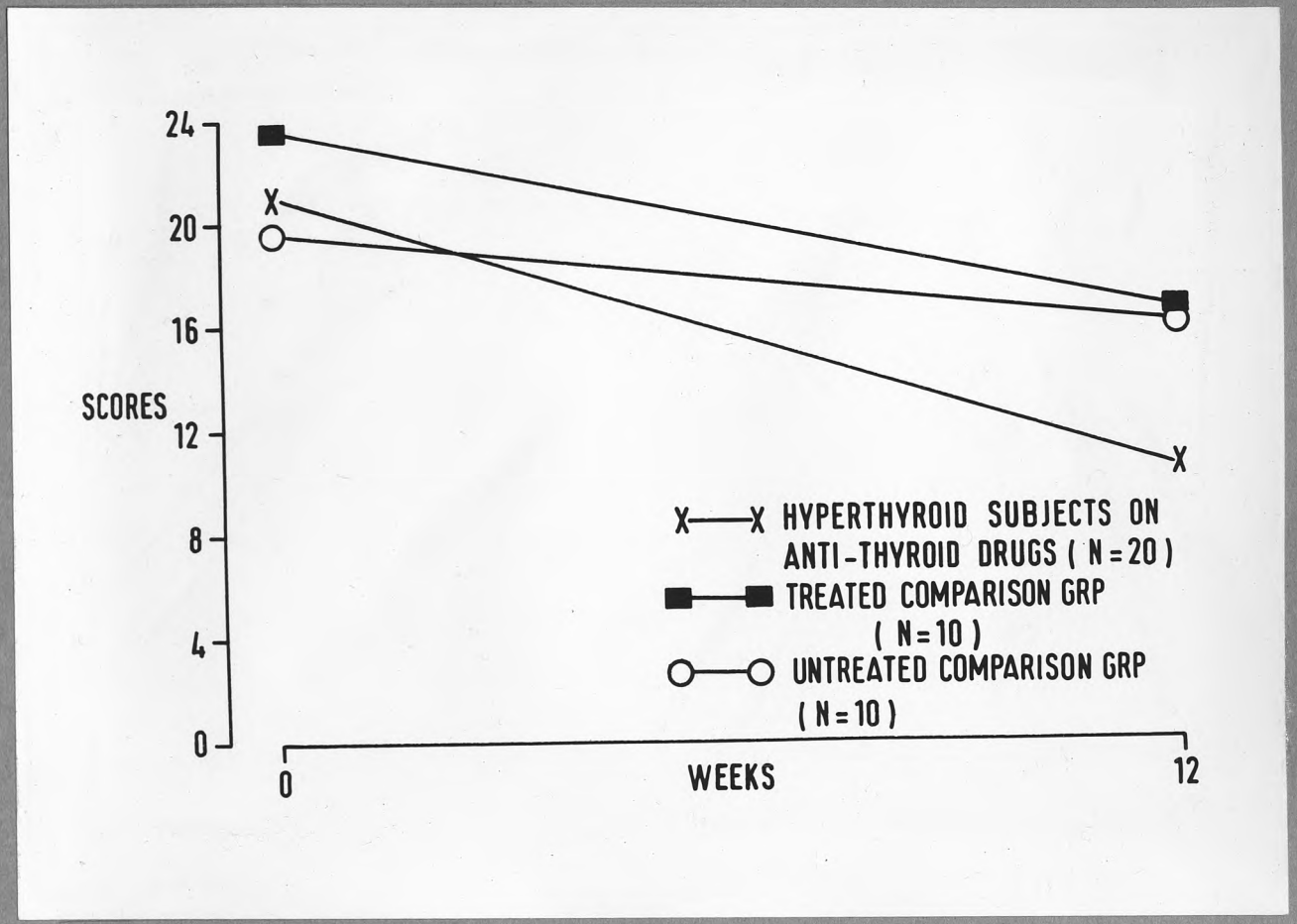


Fig. 3.12 Showing the effect of treatment on the level of anxiety, using the median scores on the Taylor Manifest Anxiety Scale.

It was however noted that the pre-treatment median for the treated comparison group was 23.5 (c.f. 19.5 for the untreated comparison group). Indicating that the level of anxiety in this group was worse than that in the untreated group.

Some tests operate on a uni-directional scale, and identify people as normal or abnormal if they score below or above a given point on the scale. Two examples of such instruments were used in this study viz., the C.M.I. and the T.M.A.S. As the distribution of scores is then skewed, it is often more meaningful-when using such tests - to use the centile rather than the mean scores to illustrate the characteristics of the population under study. Also, in longitudinal studies, as in the present one, the changes in groups' scores - relative to the test's critical score - become more apparent.

9. Self-Rating for Anxiety on the Visual Analogue Scale.

Figs. 3.13 to 3.15 show the trends in the mean daily ratings by the subjects of the various groups. These trends have been examined by regression analyses, the lines representing the regression equations and their 95 per cent confidence limits being shown in each diagram. It will be seen that both the hyperthyroid and the treated comparison groups show a trend in the improvement direction in their self rating. These trends were significant beyond the 0.1 per cent level. An analysis of covariance (Table 3.22) between these two groups shows that the trend shown by the treated comparison

group /

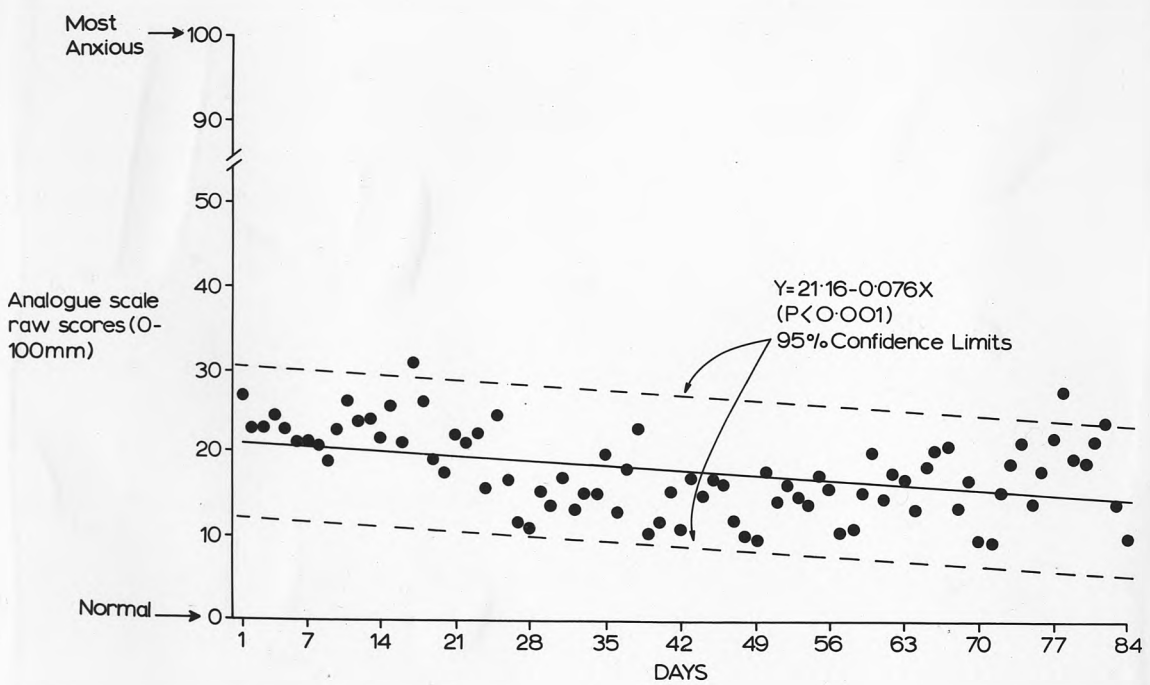


Fig. 3.13 Showing the mean self-rated anxiety levels (Visual Analogue Scale) of 20 hyperthyroid subjects during treatment with anti-thyroid drugs. The trend towards normality is significant beyond the 0.1 per cent level.

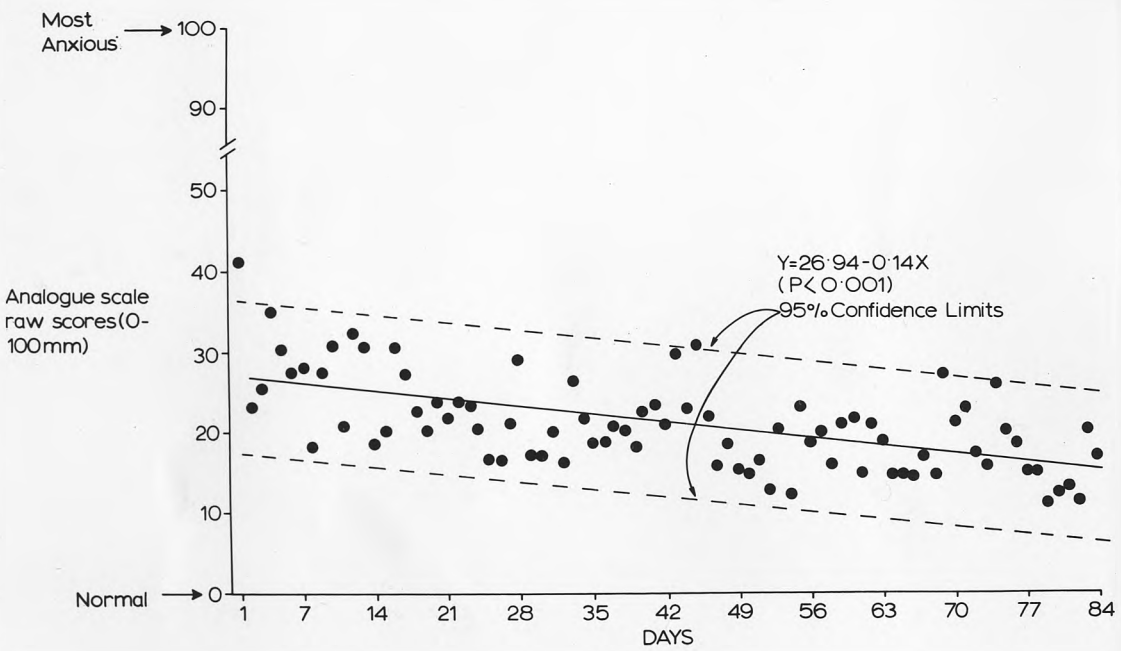


Fig. 3.14 Showing the mean self-rated anxiety levels (Visual Analogue Scale) of 10 Comparison Group subjects on treatment with psychotropic drugs. The trend towards normality is significant beyond the 0.1 per cent level.

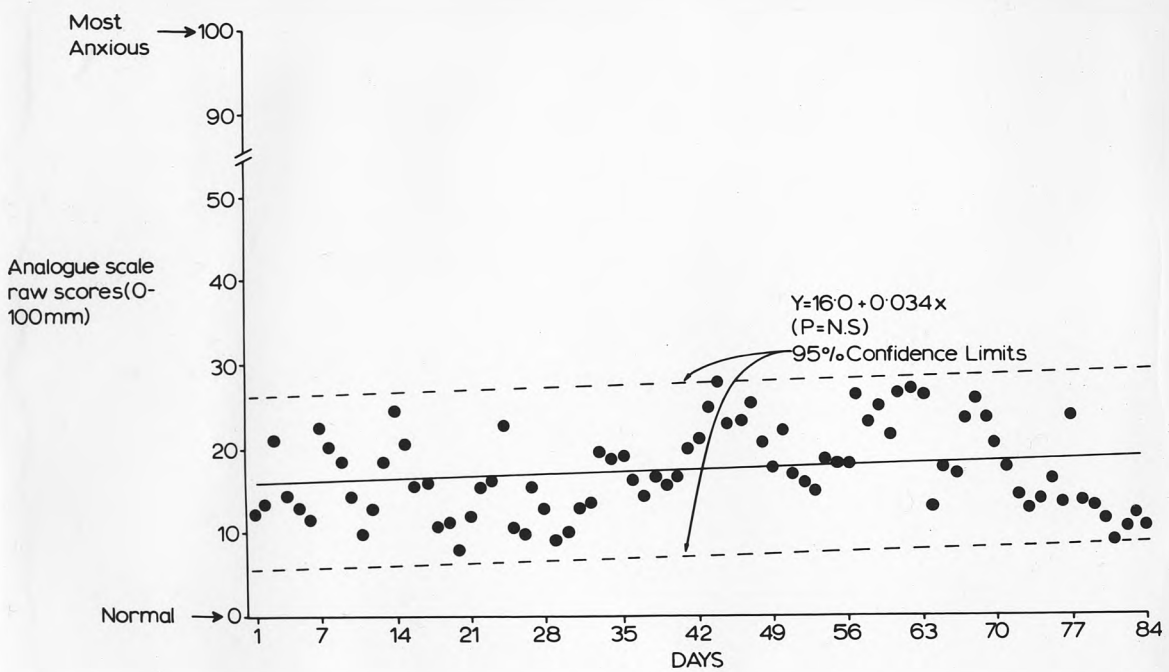


Fig. 3.15 Showing the mean self-rated anxiety levels (Visual Analogue Scale) of 10 Comparison group subjects not receiving any drug. There is a noticeable trend towards deterioration in level of anxiety.

| Source | Deviation from Regression | Degrees of Freedom | Mean Square | F | P |
|---|---|---|---|---|---|
| 1. Hyperthyroid Group | 1674.39 | 82 | 20.42 | | |
| 2. Comparison Group | 1736.03 | 82 | 21.17 | | |
| 3. Within | 3410.42 | 164 | 20.80 | | |
| 4. Regression Coefficient | 103.88 | 1 | 103.88 | 4.995 | <0.05 |
| 5. Common | 3514.30 | 165 | 21.29 | | |

Table 3.22 Table of Analysis of Covariance of the regression curves for self-rated levels of anxiety - Visual Analogue Scale. The hyperthyroid group is compared in this Table with the comparison group on psychotropic drugs.

group was significantly greater than that by the hyperthyroid group ($F = 4.995$; d.f. = 1/164; $P < 0.0.5$). The trend in the mean self-rating by the untreated comparison group was, in contrast to the other two groups, in the non-improvement direction. This trend was not statistically significant.

In order to assess changes in variability of the self-rated levels of anxiety, the mean square successive differences (M.S.S.D.) - see page 63 - were computed for the first 10 days and the last 10 days of the 84 days of observations. The M.S.S.D. for the first 10 days was designated the pre-treatment M.S.S.D., while that for the last 10 days represented the post-treatment M.S.S.D. Table 3.23 shows the mean pre-treatment M.S.S.D. for the hyperthyroid and the comparison groups. Since the distributions were grossly skewed, a non-parametric test - the Mann-Whitney 'U' test - was used to assess the significance of the difference between the two means. This difference was not statistically significant.

The hyperthyroid group was a more heterogeneous group when compared with the comparison group ($F = 3.43$; d.f. = 19/19; $P < 0.01$). And this pattern appeared to remain unchanged with treatment. The drop in the mean M.S.S.D. to 337.0 (Table 3.24) was not significant, and neither was the change in the median from 183.6 to 10.0. Only the treated comparison group appeared to have shown a statistically significant drop in their M.S.S.D., and also in their median which shifted from 291.1 to 17.5.

The /

| Scale | Hyperthyroid Group N = 20 | | Comparison Group N = 20 | | Significance of Difference * |
|---|---|---|---|---|---|
| | Mean | s.d. | Mean | s.d. | |
| M.S.S.D. | 420.5 | 658.4 | 336.6 | 355.1 | U=196 ; P=N.S. |

* Mann-Whitney 'U' Test two-tailed.

Table 3.23 Showing the mean pre-treatment M.S.S.D., and the standard deviation, for hyperthyroid and comparison groups.

| Scale | Group | N | 'Pre - Treatment' Mean | s.d. | 'Post - Treatment' Mean | s.d. | Significance of Differences* |
|---|---|---|---|---|---|---|---|
| M.S.S.D. | Hyperthyroid Group | 20 | 420.5 | 658.4 | 337.0 | 628.6 | U=194 ; P=N.S. |
| | Treated Comparison Group | 10 | 364.0 | 268.1 | 115.6 | 189.6 | U=13 ; P<0.02 |
| | Untreated Comparison Group | 10 | 309.2 | 439.0 | 132.5 | 231.2 | U=38 ; P=N.S. |

*Mann-Whitney 'U' Test, two-tailed.

Table 3.24 The effect of treatment on the mean M.S.S.D.

The Von-Newmann Ratio (V.N.R.) - see page 63 - calculated for the entire 84-day period of observation showed that more hyperthyroid subjects tended to have a higher V.N.R. (median = 1.26) than either the treated comparison subjects (median - 1.13) or the untreated comparison subjects (median 1.11). This would seem to indicate that the trend in the hyperthyroid group was more variable; but these differences failed to reach the 5 per cent level of significance on the median test.

# CHAPTER V

## D I S C U S S I O N

(A) The Comparison Group :

The main focus of comparison aimed at in this thesis is two-fold. Firstly, before treatment was ever started, it was informative to compare and contrast the hyperthyroid subjects on the one hand with all the comparison subjects as a group on the other. One advantage of this was the possibility afforded of studying the psychopathology in hyperthyroidism while the disease was still very active, and comparing it with the psychopathology of a group of patients, with the presenting symptom, but not due to hyperthyroidism; presumably these symptoms were attributable to minor functional neurotic states. Secondly, the focus of the longitudinal study - during treatment - was on those changes in psychopathology which appear to be concomitant with the return to normal of the endocrine disorder. Since the hyperthyroid subjects were at no time given psychotropic drugs or any form of psychiatric treatment, the main comparison group in this study should be those subjects who received no psychotropic drugs. The comparison group which had psychotropic drugs served as a comparison group more for the untreated group than for the hyperthyroid group, and the variable being compared between them was the effect of psychotropic treatment.

The allocation of a subject to either of the treated or untreated comparison group was not random.

It /

It might therefore be argued that the changes in psychopathology observed in these groups could not be entirely attributable to the treatment given to one of them, but in part to some unknown factors associated with the sampling. If such factors were existent in this study, their effect on the outcome of treatment was probably counterbalanced by the effect one factor known to be associated with the sampling. This was the fact that those who received psychotropic drugs were those who appeared to be more disturbed as evidenced by the degree of distress communicated, and their clinical assessment at consultation. It would be seen that the treated comparison group consistently had higher mean values on the various psychometric tests used in this study, though differences were not statistically significant. But when the communication of their anxiety on the visual analogue scale was compared for the first day (i.e. before the effect of treatment could become appreciable), the untreated comparison subjects communicated a highly significantly lower level of anxiety than their treated counterparts ('t' = 3.27; d.f. = 18; $P < 0.01$).

It appears therefore reasonable to conclude that the treatment given to the treated control group was to a degree beneficial. The subjects in this group appeared to be worse off than their counterparts at the beginning, and yet they improved. There was a definite and statistically significant trend towards improvement in their communication on the visual analogue scale (Fig. 3.14) in contrast to the untreated comparison subjects who would appear to be getting worse (Fig. 3.15). There was also a detectable trend in the mean or median scores on the C.M.I. and T.M.A.S. for the untreated comparison group to be lower by the end of the study. But this, as would be seen in some of the results, was not as striking as was the trend in the treated comparison group.

Such /

Such variation in scores for what was theoretically an unchanged situation might be due to a number of factors. These factors may be considered under two main, though not exhaustive, categories :

1. Factors inherent in the measuring instruments.
2. Factors related to the natural history of neurotic illnesses.

1. Factors inherent in the Measuring Instruments.

The psychometric tests are not entirely perfect in their test-retest reliability. Table 4.1 gives the correlations, where available, obtained by the authors of the psychometric tests used. The correlations between the pre-, and post-study scores of the untreated comparison group are given in the same table. Comparative figures for groups of subjects with active pathological states are not often encountered. It can be seen then that in groups of subjects with or without any evidence of pathology, the psychometric instruments tend to lose their sensitivity when they are repeatedly applied.

2. Factors related to the natural history of neurotic illnesses:

Untreated neurotic illnesses, like some physical diseases, are known to show spontaneous remission after varying lengths of time. Neurotic illnesses can exhibit extremely long courses as well as very brief courses. An average duration of between one and two years has been estimated for the natural history of neurotic illnesses (Eysenck, 1960). To support this estimate, Eysenck quoted a work by Shepherd and Gruenberg who seemed to have suggested 100 per cent spontaneous remission after two years.

There /

| Test | Scale | Test Author's Findings (Normal Subjects) | Present Study ( Untreated ) (Neurotic Subjects) |
|---|---|---|---|
| 1. C.M.I (Brodman et al 1949 ) | | | |
| | (a) Total | † | 0.80 * |
| | (b) M-R | † | 0.80 * |
| 2. T.M.A.S (Taylor, 1953) | | | |
| | (a) Total | 0.88 + | 0.81 * |

+ 4 weeks test-retest reliability; * 12 weeks test-retest reliability

† No figures published.

Table 4.1 Showing the test-retest reliability of the psychometric instruments (questionnaire types) used in this study.

There are people who would not admit the occurrence of spontaneous remission but it is common teaching that some patients on admission waiting lists have often recovered spontaneously before the time they were expected to be admitted. Also related to the natural course of neurotic illness is a factor observed in this study and to which there seemed no readily available reference in the literature. This was the periodicity in the severity of the subject's illness when assessed by the subject's communication of the severity of his own symptoms. Fig. 4.1 shows a typical pattern of communication manifested by some of the comparison subjects. It can be seen that most of the time, the subject seemed to experience only a mild to moderate degree of anxiety. But periodically, the anxiety assumed almost severe proportions. If such patterns did truly reflext the trend in the actual psychopathology, it can be seen how psychometric test scores would be bound to vary according to the point in time at which the text was administered.

It appears from the foregoing discussions that the changes in the psychopathology of the untreated comparison subjects of this study were not incompatible with the picture to be expected for any group of untreated neurotic patients. It seems therefore valid to compare them with the hyperthyroid and the treated comparison subjects.

(B) The Hyperthyroid group :

1. Skin Conductance Measures: From the results obtained in this study, it may be concluded that the psychophysiological effects of hyperthyroidism consisted of:

a. Hyperarousal.
b. Hypersensitivity.
c. Increased reactivity/responsivity.

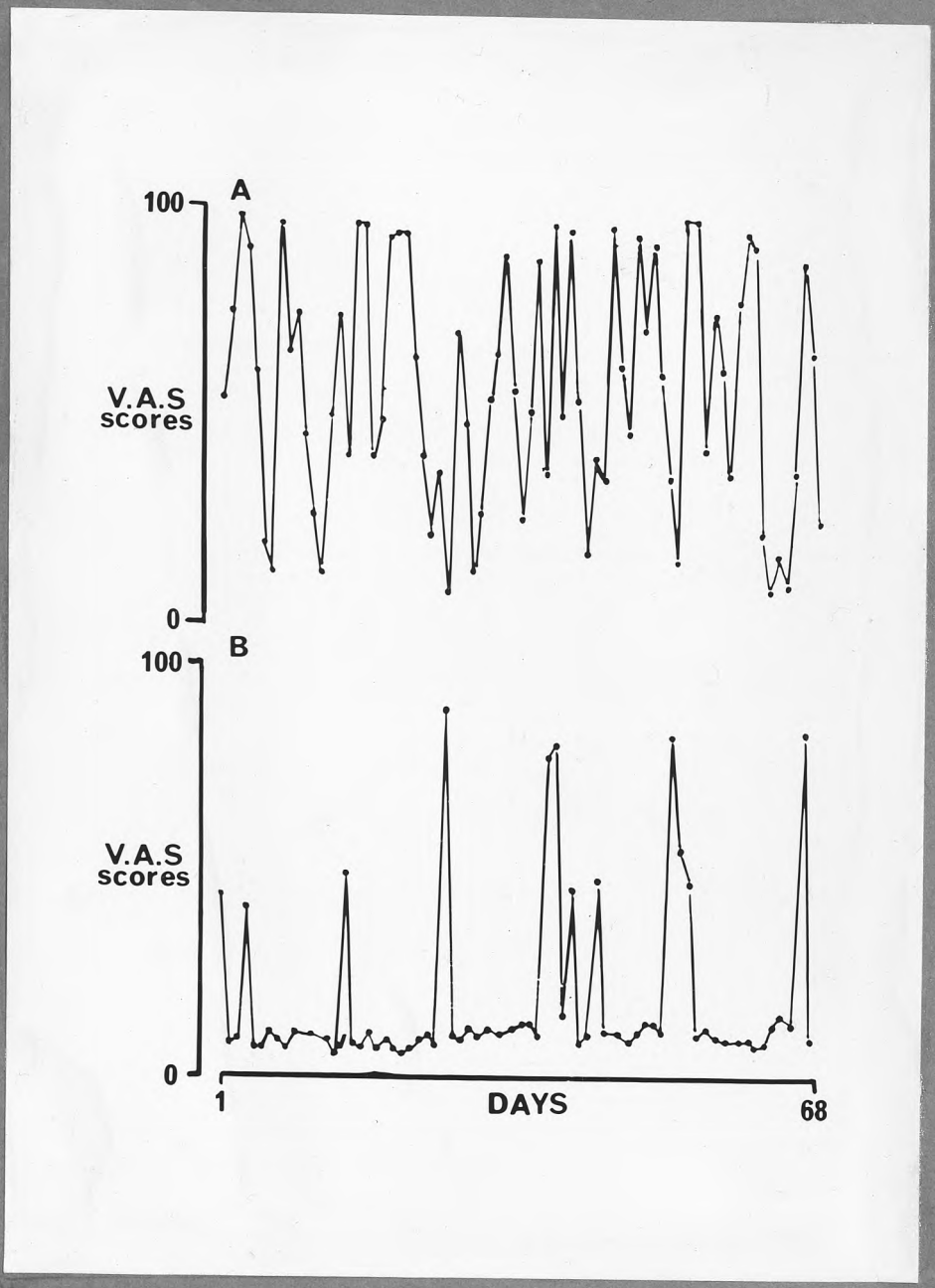


Fig. 4.1 Showing two patterns of communication of anxiety on the Visual Analogue Scale.

Pattern A was found to be more common among the hyperthyroid subjects.

Pattern B was more common among the Comparison group subjects.

Both patterns illustrate variability in levels of anxiety in the two groups of patients.
See also Fig. 2.6, and Tables 3.23 - 3.24

There seems little doubt that these effects were produced centrally. This deduction is more easily explained in terms of the various skin conductance measures than the cardiovascular ones. There was a higher skin conductance level in the hyperthyroid group; the frequency of spontaneous fluctuations was increased at the beginning of the recording session, but soon settled and the psychogalvanic reflex was larger. The hypersensitivity was inferred, but it was substantiated by the higher variability in the communication of anxiety levels on the visual analogue scale (Table 3.23, also Fig. 4.1)

There has been a tendency among physicians to assume, without experimental foundations, that the excessive sweating in hyperthyroid states was a direct consequence of the hypermetabolism present in these states. The increased energy produced would be partly dissipated as heat which in turn induced thermoregulatory processes which included sweating and peripheral vasodilation (Mason 1957 ). Although the skin of the palm and sole have the highest concentration of sweat glands in the body, Kuno (op. cit) has shown that these sweat glands do not subserve thermoregulatory function. There have been a few reports which might throw doubt on Kuno's findings. Venables (1955) in a review of these reports came to the conclusion that below a temperature of 75°F (24°C), the sweat glands of the palm and soles play no part in temperature regulation. Above this temperature, significant correlations may be obtained between temperature and palmar sweating in a small number of people. All the experiments in this study were conducted in a constant environment with a temperature of 21°C which is well below the critical temperature suggested by Venables.

Then there were the early theories which sought to explain the increased autonomic symptoms found in hyperthyroid states.

It /

It was postulated that thyroxine increased the sensitivity of sympathetic nerve endings to adrenaline and non-adrenaline. This potentiation was held to account for the increased autonomic symptoms, and the possibility of a central action was not considered. The involvement of adrenaline and non-adrenaline was supported on clinical grounds by the extreme similarity between the clinical manifestations of phaeochromocytoma and thyrotoxicosis, and the frequent finding of thyroid gland hypertrophy in association with adrenal phaeochromocytoma. In this disease, as in thyrotoxicosis, there is paroxysmal tachycardia, profuse perspiration, dyspnoea, and history of irregular menstrual functions.

The experimental investigations of the thyroid hormone-catecholamine potentiation theory were unfortunately confined entirely to the cardiovascular system. And their results were, without caution, extrapolated to the rest of the autonomic nervous system. These investigations will be considered in more detail in relation to the cardiovascular findings in this study. For the present, their underlying theory interests us mainly because it places the anatomical site of action peripherally and, in addition, involves only one group of neurotransmitters - the catecholamines. The palmar sweat glands are subserved by cholinergic sympathetic fibres. Lader and Montagu (1962) abolished the P.G.R. when they instilled atropine by iontophoresis into the palmar skin of the thumb. Their finding has shown conclusively that the catecholamines are not involved in the peripheral mechanisms of the skin conductance and the P.G.R.

There have been some reports with consistently similar findings which would strongly indicate that the mechanism of the autonomic symptoms of

hyperthyroidism might be more central than peripheral. Rae (1944) in the earliest of these reports described a significant relief of symptoms giving spinal anaesthesia to patients with thyroid crisis, or as an adjunct to general anaesthesia for thyrotoxic patients undergoing hyperthyroidectomy. Similar findings have been observed by Knight (1945). He reported the management in this way, of a 41-year old hyperthyroid patient who was admitted to the University of Minnesota Hospitals for thyroidectomy. The first attempt at surgery was abandoned as a result of deterioration in the patient's physiology while under anaesthesia. After a stormy post-operative period, he was given a course of deep radiation therapy to the thyroid gland. This seemed to have produced a fall in this basal metabolic rate from a pre-treatment maximum of +84 per cent to +53 per cent. But it was noted that "he became somewhat restless and did not seem to acquire a mental and physical calmness". At a second attempt at surgery, he was given a spinal anaesthesia (75 mgm. procaine hydrochloride) in addition to the routinely given general anaesthesia. The spinal anaesthesia was noted to be effective up to the level of the third intercostal space. A total of four other patients were given a similar management. These were in addition to the 20 patients previously reported by Rae from the same hospital. The typical picture was described as follows, "the blood pressure and pulse run a more even and less elevated course than we expect in even less toxic patients under the usual regime without spinal anaesthesia. The awakening is quieter, the patients seem more content and less mentally active". Knight pointed out that for this effect to be achieved, the spinal anaesthesia must be so planned to produce anaesthesia up to approximately fifth or perhaps the fourth thoracic segment.

The /

The use of spinal anaesthesia like this was extended to pre-operative hyperthyroid states in which the hyperactivity was excessive, and to post-operative thyroid crises. The results were exactly identical.

Brewster (1956), in the most recent report available with relevance to this question, gave a total epidural spinal block to dogs which have been rendered hyperthyroid by thyroid feeding. Following a laminectomy at the level of the second or third lumbar vertebrae, he introduced catheters to varying levels of the spinal column, the highest being the level of the first thoracic segment. He then injected a solution of 0.45 per cent procaine hydrochloride into the epidural space to produce what amounted to a total epidural pre-ganglionic sympathetic block. He found that the physiological over-activity induced by the thyroid feeding was abolished.

Clinical and laboratory findings, such as these, clearly demonstrate that the physiological(-autonomic)-hyperactivity in hyperthyroidism is central rather than peripheral.

There are three reports in the literature which contain results comparable to the physiological findings in this study. The first two were from Franz Alexander and his colleagues at the Psychiatric and Psychomatic Research Institute, Los Angeles, who were interested mainly in establishing that hyperthyroid subjects reacted more profoundly to a specific emotional stimulus - threat to biological survival (Alexander et al, 1961; Flagg et al 1965). In these studies they found that a group of hyperthyroid subjects when exposed to a stressful film (Wages of Fear) lasting 100 minutes, exhibited "a progressive decrease in GSR throughout the measurement period, or showed little or no change from

their initial resting levels". In contrast, their control subjects (apparently normal-healthy-individuals) "showed a progressive increase in resistance (decreased skin conductance) beyond the initial resting levels". There is no detailed account of how the skin resistance was measured, and no figures were made available in the first report to indicate the resistance level. The terminology used was also rather confusing. For example when they referred to the G.S.R. (galvanic skin response) they meant the skin resistance level. And they talked about 'adaptation' to the film when they apparently meant 'habituation' (see page 34 ). The progressive decrease in the skin resistance level would represent a tonic arousal. Their results when interpreted this way, would be comparable to the findings on the skin conductance level in this study.

The third report concerned the effect of thyroid hormone on the startle reflex in the rat (Korn 1966). Tri-iodothyronine ($T_3$) was given intraperitoneally to a group of rats, and methimazole to another group. Thyroid function, monitored by measuring the heart rate, was deemed to have been increased as a result of the $T_3$ injection, and decreased by methimazole. No mention was made as to how the startle response, provoked by firing a blank starting pistol, was quantified and measured. It was found, however, that both 'hypo' and 'hyperthyroid' rats showed larger responses than controls. In a second experiment, he concluded that the $T_3$ injection led to the maintenance of the startle response at high levels over successive tests, although this level is not significantly greater than that exhibited by normal rats in initial exposure to the situation.

It is not known for certain exactly by what mechanisms thyroid hormones influence the central nervous system.

The /

The hypothalamus is intimately involved in the regulation of thyroid function. However, there appears to be no such thing as a thyroxine-sensitive 'receptor' centre in the hypothalamus (von Euler et al 1956; Harrison 1961). Electroencephalographic studies have shown that, in general, administration of thyroid hormones increase the frequency of the alpha rhythm, thereby implicating arousal mechanism and cortical activity. (Rubin et al 1937; Ross et al 1939; Condon et al 1954; Wilson et al 1964). In addition, from our present state of knowledge about the neuropsychological basis of arousal and P.G.R. phenomena, one might be tempted to suggest that the brain stem reticular formation is the part of the brain mostly affected.

The results of this study however also implicate the central autonomic nervous system. This system is more widely distributed in the brain than is usually assumed by some people. Livingston (1969), in a review, has pointed out that the central autonomic nervous system is not confined to the hypothalamus. It involves parts of the frontal and limbic cortex, and the mesencephalic reticular system. It would appear that it was the sympathetic division of the central autonomic nervous system which was functionally over-active. There is evidence that the autonomic effects of the thyroid hormones are mediated mainly by the sympathetic nervous division (Gaffney et al 1961; Waldstein 1966). This would explain (a) the higher conductance level and other features observed, (b) the similarity between the clinical manifestations of hyper-thyroidism and phaechromocytoma, and (c) the dilated pupil often found in hyperthyroid patients.

Gellhorn ( 1968) in a series of neurophysiological experiments showed that the central autonomic nervous system was always "tuned" ergotropically (sympathetic) or trophotropically (parasympathetic), using the terms employed by Hess to divide the system into its two components. When the autonomic system was "tuned" in one direction, there was a reciprocal reduction of activity in the other direction, and the responses of the dominantly "tuned" component were exaggerated. Sometimes the dominantly "tuned" component was so highly "tuned" that it "spilled" over into the reciprocally "un-tuned" system thus giving paradoxical responses. He hypothesised that a stage could be reached in which both the ergotropic and the trophotropic systems would be equally highly "tuned". In such a situation, autonomic imbalance would occur. This might be the neurophysiological explanation of the neurotic conflict, and emotional disorders in general. Gellhorn's findings would adequately account for most of the results obtained in this study. Thus hyperthyroidism would have produced an ergotropic "tuning" of the central autonomic nervous system. This would be responsible for the increased reactivity observed; and since the ergotropic system is the predominant, the trophotropic system would be reciprocally inactive. This might also explain the remarkable rarity of peptic ulcer (generally regarded as vagal or trophotropic) in association with thyrotoxicosis (Levitt 1954).

2. <u>The Cardiovascular findings.</u> The cardiovascular aspects of hyperthyroidism deserve to be considered separately. Much research has been done in this area, provoked mainly by the controversy over thyroid-catecholamine relationships.

The /

The possibility of psychophysiological involvement in the phenomenon observed may not be so apparent as was the case with the skin conductance measures.

Most of the studies reported have been concerned more with the cardiac and much less with the vascular changes. The techniques were based on the pharmacological principles of autonomic blockade. Since the different parts of the cardiovascular system have a similar pattern of autonomic innervation, the results about one part may be extrapolated to the other with reasonable confidence.

The reviews by Harrison (1964), and Waldstein (1966), summarised the earlier works in this field up to 1965. Harrison (1964) had proposed that the stimulation of the heart in thyroid overactivity was due to potentiation of the cardiac action of catecholamines by the excessive thyroxine in circulation. More recent work would however show that this is not entirely true. Most of the earlier studies, for example, failed to take into account dose-response relationships, and therefore did not analyse these. The experiments were usually conducted in vitro on isolated organs such as perfusing arteries with solutions of thyroxine and inducing contractions by adding adrenaline. The more recent studies have sought to examine the cardiovascular effects of thyroid hormones by in vivo experiments. The results of some of these studies, in animals, would indicate that hyperthyroid tachycardia could not be accounted for entirely by thyroid hormone potentiation of the catecholamines (van der Schoot et al 1965; Margolius et al 1965). This observation has also been confirmed with studies in man by Wilson et al (1966), and Aoki et al (1967).

Aoki /

Aoki administered triiodo-thyronine ($T_3$) parenterally to human volunteers in doses ranging up to 500 micrograms daily until a definite hypermetabolic state was established. This was confirmed by P.B.I. estimations. Unlike Wilson et al (op. cit) he used the more naturally occurring catecholamines - adrenaline and non-adrenaline, and administered these in various doses to his hypermetabolic subjects and controls. The changes in cardiac function were then measured. Although adrenaline by itself showed an overall dose-related response in the amount of cardio-vascular changes, there was no significant difference by the addition of $T_3$. Similarly $T_3$ did not alter the effect of the nor-adrenaline. The results obtained by Aoki might not be entirely logical. It could be argued that the sympathetic nervous system was already maximally stimulated as a result of the induced hypermetabolic state. If this were so, the Law of Initial Value (Wilder 1957) would predict that further stimulation by the catecholamines would only produce little and non-appreciable effect. And this was exactly what Aoki found in his study.

In 1966, Anthony Jose reported the results of his work on the effect of complete autonomic blockade on the heart rate and cardiac function in man. His aim was to produce, in vivo, in the intact subject, an experimental situation resembling cardiac isolation. By giving doses of propranolol 0.2 mg/kg. body weight and atropine 0.04 mg/kg. body weight as a single intravenous injection over two minutes, he could block the natural sympathetic and parasympathetic (vagal) stimuli to the heart. The effect, using the doses stated, lasted up to 20 minutes. The heart rate (chronotropic effect) after such a block fell to a level which he

called /

called the 'intrinsic heart rate (IHR)'. In normal adults aged between 20 and 30 years the IHR averages 104.4/min. (S.D. $\pm$ 7.4) decreasing with age to 92.4 (S.D. $\pm$ 9.0) by between 45 to 55 years of age. The IHR did not appear to be related to sex or to body weight. He found that in 12 thyrotoxic patients, the IHR was markedly raised in 6 but markedly depressed in 2 without any clear relation to the degree of cardiac disability present. This finding of altered IHR in hyperthyroid patients was the first pointer to the possible existence of direct action by the thyroid hormones on cardiac tissue.

McDevitt et al (1968) employed Jose's technique to investigate the question of thyroid-catecholamine effect on cardiac function. He studied hyperthyroid patients who had received no previous treatment at all for their disease, or at least in the previous 6 months. He also had a comparative group of hypothyroid patients, but no normal subjects. All the patients were in sinus rhythm; and he took the heart rate 5 minutes after completion of injection as the IHR. He found that the mean IHR in the hyperthyroid patients was significantly higher than for hypothyroid patients, and concluded that the tachycardia associated with the former was a result of direct stimulation of cardiac tissue by thyroid hormones and not via the autonomic system. Such a conclusion as this needs to be treated with caution. There was no comparison with euthyroid patients, and it was not demonstrated that the IHR in hyperthyroidism was significantly higher than in an euthyroid state.

Hill and Turner (1968) compared the IHR in 25 hyperthyroid patients with 6 hypothyroid and 16 euthyroid subjects. They confirmed the negative relationship between IHR and age made by Jose (op. cit).

They /

They therefore adjusted for age in the analysis of their data. They found that the mean IHR for hyperthyroid patients was significantly higher ($P < 0.01$) than normal subjects while that for the hypothyroid patients was lower but not significantly so ($P < 0.1$). They however observed that there was a much wider scatter of the IHR in the hyperthyroid group, and suggested that this alone could not be responsible for hyperthyroidic tachycardia. This suggestion was reinforced by the finding that the change in IHR ranged from 0 - 16 beats/min. after treatment.

In supporting the observations made by Hill and Turner, there is evidence in the literature to show that the role of thyroid-potentiated catecholamine action cannot be ruled out completely in the tachycardia of hyperthyroidism. It is true that atria removed from hyperthyroid animals beat more rapidly in vitro than do those from normal animals. But this is by no means a universal observation. Other workers have observed decreased contractility rather than increased (for example van der Schoot & Moran 1965). There is no evidence that isolated organs lose their catecholamine content much more rapidly enough to rule out catecholamine potentiation. It has been shown on the other hand that a significant decrease occurs in the monoamine oxidase (M.A.O.) concentration in the liver and blood vessels of thyroxine-injected animals (Spinks and Burn 1952; Spinks 1952). This factor, if anything, should retard rather than accelerate the breakdown of the catecholamines in the tissue. Bacq (1949) has pointed out that, theoretically, thyroxine by virtue of its molecular structure, could inhibit the activity of M.A.O. Also, Carrier et al (1961) and Prange et al (1962) have shown that there is increased toxicity of M.A.O.-Inhibitors, and the tricyclic anti-depressant drugs in thyrotoxic animals.

Shepherd (1963) suggested that part of the increased forearm blood flow in hyperthyroidism might be the consequence of two factors :-

(a) Increased metabolic rate causing a demand for faster circulation of blood to different parts of the body especially muscular tissues;

(b) Reflex dilatation of the skin vessels for thermo-regulatory purposes.

The second factor may not be so important although its role cannot be neglected. The bulk of the forearm blood flow is accounted for by muscle blood flow. The nervous control of the muscle vessels - in the resting state - is relatively weak: maintained by nor-adrenergic vaso-constrictor, and cholinergic vasodilator sympathetic fibres. During emotional stress, the vasodilator fibres become very active and several-fold increases in forearm blood flow may occur (Barcroft et al 1960). In contrast, the vessels in the forearm skin have nor-adrenergic vaso-constrictor nerves; the vasodilatation is due - not to nervous - but to a humoral mechanism involving bradykinin, and only occurs under exposure to high ambient temperatures with sweating.

It seems therefore, from this discussion, that the cardiovascular changes associated with hyperthyroidism would be due to a combination of the following factors :-

1. Direct effect of thyroid hormone on the heart tissue.

2. Increases stimulation via the sympathetic nervous system, due either directly to hyperactivity centrally, or to potentiation of the catecholamines by thyroid hormone peripherally, or both.

3. /

3. Consequences of the increased metabolism - greater demands for blood by the entire body for oxygen, removal of catabolic products, and thermo-regulation.

4. The effect of the emotional stress associated with the disease.

3. General Psychiatric Morbidity. From the observations made on page both the scores on the total scale and the M - R scale of the C.M.I. appear to be valid measures of psychiatric morbidity in this study. One would normally expect scores on the sections A to L of the C.M.I. to reflect the organic aspect of the disease only. That this was not so might be explained by (a) the presence of sections I and L; and (b) some questions in the other sections which relate to functional, rather than organic, symptoms. In addition other questions relate to symptoms capable of having either a functional (psychological) basis, or an organic basis. A sample list of these questions are quoted below as an illustration, the numbers appended to them being the actual numbers of the questions in the Index.

11. Do you feel a choking lump in your throat?

12. Do you suffer from asthma?

13. Has a doctor ever said your blood pressure was too high?

92. Do you bite your nails badly?

96. Were you a bed-wetter between the ages of 8 and 14?

Hamilton /

Hamilton et al (1962) found that high M - R scores were associated with more numerous physical symptoms, and drew attention to the significance of "functional somatic symptoms" in validating the total scores on the Index as a measure of psychiatric morbidity. They found as in most studies that there was a higher score of functional symptoms among their female subjects when compared to the male. The significance of 'functional somatic symptoms' has given the C.M.I. a respectable degree of reliability in assessing psychiatric morbidity and patterns of feelings in the so called 'psychosomatic diseases'. Thus it was used in asthma (Leigh and Marley 1960), in relation to myocardial infarction (Verghese 1970), and thyrotoxicosis (Paykel 1966).

From the results obtained in this study there seems to be a considerable amount of psychiatric morbidity associated with hyperthyroidism. The proportion of patients identified as psychiatrically ill was smaller but not significantly different from that of a control group of neurotic patients. The distribution of scores about the means in the two groups were, however, very different. The hyperthyroid group appeared to be a much more heterogeneous group than the control group. Their scores varied over a wider range with a consequently larger variance. Unlike some of the psychophysiological indices which were uniformly raised in the hyperthyroid patients, high scores on the C.M.I. appeared to be limited to only a proportion of the group. It therefore follows that psychiatric illness in hyperthyroidism was not always an accompaniment of the psychophysiological abnormality found with the disease. It is possible that these differences between the hyperthyroid and the control groups could have been more

pronounced had the later group been composed of patients with more severe or sustained neurotic symptoms.

Paykel (op. cit) administered the C.M.I. to a group of 35 thyrotoxic patients who had had successful treatment of their illness 3-4 years previously. Using the scores on the M - R scale only, he found their mean score to be 9.6 (s.d. = 8.7). There was no significant difference between this group and a matched control group of 35 subjects without history of hyperthyroidism but who had had subtotal thyroidectomy for simple goitre. The mean value obtained by Paykel is comparable to the mean of 9.2 (s.d. 12.0) obtained for the hyperthyroid patients in this study, after treatment for a contrastingly shorter period of 12 weeks.

It is apparent therefore that, to some extent, the psychiatric morbidity accompanying hyperthyroidism tended to be improved as the underlying endocrinological disorder was corrected. This finding again contradicts the assertion by Moschowitz (op. cit) that hyperthyroidism was an aggravated form of neurocirculatory asthenia, and that the symptoms persisted for life but in a less severe form when the hyperthyroidism had been treated.

4. Anxiety. Earlier clinical descriptions of hyperthyroidism have tended to over-emphasise the degree of anxiety present in the disease. It was believed, from the clinical appearance of the patients, that the disease was of a nervous nature with anxiety as the predominating emotional state. The implication of these clinical impressions and beliefs was that all hyperthyroid patients suffered from an extremely severe degree of anxiety.

These /

These assumptions were never tested for confirmation or refutation since the more modern psychometric tests did not exist then. Even since the development of these tests, proper and controlled studies have not been reported. Wayne (1954), basing his assessment on clinical studies, found that only about 60 per cent of thyrotoxic patients had nervous symptoms. He compared this with the proportion of 20-25 per cent of matched control subjects who complained of nervous symptoms.

The scores on the Taylor's Manifest Anxiety Scale (T.M.A.S.) was in accordance with the findings on the C.M.I. Using a score of 14 on the T.M.A.S. as the critical score above which anxiety may be regarded as abnormally high, 70 per cent of the hyperthyroid patients were found to have scores above this point. The proportion in the control group was 80 per cent. The proportions of 70 per cent (T.M.A.S.), and 60 per cent (C.M.I.) compare fairly well with Wayne's estimate of "about 60 per cent". They reinforce the proposition which has been made earlier that psychiatric morbidity was not necessarily an invariable accompaniment of the over-activity of the thyroid gland.

It is possible that the C.M.I. and the T.M.A.S. were reflecting the same abnormality - anxiety in this study. The C.M.I. measures patterns of feelings, and psychiatric morbidity in general, and no attempt has been made in this study to diagnose forms of psychiatric illness which might have been present. Some of the subjects might well have been suffering from a depressive illness. Anxiety is however commonly associated with most psychiatric illness, and could have partly accounted for the scores on the C.M.I. A rank order correlation of 0.82 was obtained between T.M.A.S. and the C.M.I. scores.

The /

The observation of the tendency by the patients to be relieved of their distress and feelings - reported as anxiety - concommitantly as the improvement in their endocrine disorder would suggest that the two events are related in some way. The patients had received no form of psychiatric treatment beyond the possible effect of the contact with the experimenter necessary for the tests to be carried out. It would therefore seem that the anxiety developed in the first place in relation to the hyperthyroidism. The exact mode of the development of such anxiety is unknown, and attempts to explain it could only amount to speculation.

# CHAPTER VI

## CONCLUSIONS

1. In this study designed to study - phenomenologically - the mood states associated with hyperthyroidism, two levels of abnormalities were found; the psychophysiological level, and the subjective feeling state level.

2. At the psychophysiological level, the abnormalities which could be attributed to the hyperthyroidism were (a) hyperarousal, (b) hypersensitivity and (c) increased reactivity or responsivity.

3. The psycho-galvanic reflex of most of the hyperthyroid patients habituated to a repeated standard stimulus. In this respect, they differed from patients with anxiety neurosis.

4. There was a tendency for the abnormalities described above to improve as the underlying endocrine disorder was treated.

5. At the subjective feeling state level - assessed by the psychometric tests - there were indications of a moderately severe degree of psychiatric morbidity and high level of anxiety. There was no difference between the hyperthyroid group and the Comparison group.

6. The hypersensitivity, and increased reactivity found at the psychophysiological level appeared to have been reflected in the subjective feeling states of the patients - when judged by the pattern of communication of their anxiety on the Visual Analogue Scale.

7. There was also a trend towards normality in the level of anxiety and general psychiatric morbidity as the hyperthyroidism was treated.

# A P P E N D IX  I

Text of the Tape-recorded speech played back to each subject during the first attendance at the Psychophysiological Laboratory.

"The test we are going to do with you is absolutely straight-forward so far as you are concerned, and it will cause you no difficulty or trouble at all. You will simply be asked to sit in a comfortable chair and a number of wires will be lightly fastened to you. You will feel nothing through these wires - no shocks or anything else.

The test is in two main parts, each lasting about half an hour or so. During the first part, you will simply be sitting in a quiet room, and you should just relax and take it easy. After the first few minutes, you will hear a fairly loud sound lasting one second. Don't worry about this; you don't have to do anything at all about it. This sound will be repeated at intervals during the rest of this first part.

So that we don't affect the measurements in any way, we avoid coming into the room where you will be sitting. But we are in complete contact with you all the time by means of an intercom system. If you say anything to us, we can hear you, and we can talk to you without having to come into the room. Naturally, once the test has started, we hope you'll not need to say anything, so we can complete the test as quickly as possible.

During the second part of the test, we make a special measurement of your left forearm, simply by asking you to place it in a water-bath which we fill with tepid water. We ask you to lie down comfortably on a couch while we make these measurements; and it is important that you should try to relax as much as possible as you lie there.

Finally /

Finally, we will be asking you to fill in one or two questionnaires that will help us to make best use of the results of the laboratory tests. Well, that is all I need to say. If you have any questions to ask at all, please do not hesitate to do so. If you'd like us to explain anything again, we shall be very happy to do so. As I said before, the whole test is simple as far as you are concerned, and should not upset you at all."

# A P P E N D I X  II

Specimen copies of the Psychometric Tests used in this Study.

1. The Cornell Medical Index.

2. The Taylor Manifest Anxiety Scale.

History Number_____

(MEN)

# CORNELL MEDICAL INDEX
# HEALTH QUESTIONNAIRE

Date_____

Print Your Name_____ Your Home Address_____

How Old Are You?_____ Circle If You Are . . Single, Married, Widowed, Separated, Divorced.

Circle the Highest Year You Reached In School | 1 2 3 4 5 6 7 8 | Elementary School | 1 2 3 4 | High | 1 2 3 4 | College

What Is Your Occupation?_____

**Directions:** This questionnaire is for ***MEN ONLY.***
If you can answer **YES** to the question asked, put a circle around the (Yes)
If you have to answer **NO** to the question asked, put a circle around the (No)
Answer all questions. If you are not sure, guess.

**A**

1. Do you need glasses to read? ..... Yes No
2. Do you need glasses to see things at a distance? ..... Yes No
3. Has your eyesight often blacked out completely? ..... Yes No
4. Do your eyes continually blink or water? ..... Yes No
5. Do you often have bad pains in your eyes? ... Yes No
6. Are your eyes often red or inflamed? ..... Yes No
7. Are you hard of hearing? ..... Yes No
8. Have you ever had a bad running ear? ..... Yes No
9. Do you have constant noises in your ears? ..... Yes No

**B**

10. Do you have to clear your throat frequently? Yes No
11. Do you often feel a choking lump in your throat? ..... Yes No
12. Are you often troubled with bad spells of sneezing? ..... Yes No
13. Is your nose continually stuffed up? ..... Yes No
14. Do you suffer from a constantly running nose? ..... Yes No
15. Have you at times had bad nose bleeds? ..... Yes No
16. Do you often catch severe colds? ..... Yes No
17. Do you frequently suffer from heavy chest colds? ..... Yes No
18. When you catch a cold, do you always have to go to bed? ..... Yes No
19. Do frequent colds keep you miserable all winter? ..... Yes No
20. Do you get hay fever? ..... Yes No
21. Do you suffer from asthma? ..... Yes No
22. Are you troubled by constant coughing? ..... Yes No
23. Have you ever coughed up blood? ..... Yes No
24. Do you sometimes have severe soaking sweats at night? ..... Yes No
25. Have you ever had a chronic chest condition? Yes No
26. Have you ever had T.B. (Tuberculosis)? ..... Yes No
27. Did you ever live with anyone who had T.B.? Yes No

**C**

28. Has a doctor ever said your blood pressure was too *high?* ..... Yes No
29. Has a doctor ever said your blood pressure was too *low?* ..... Yes No
30. Do you have pains in the heart or chest? ..... Yes No
31. Are you often bothered by thumping of the heart? ..... Yes No
32. Does your heart often race like mad? ..... Yes No
33. Do you often have difficulty in breathing? ... Yes No
34. Do you get out of breath long before anyone else? ..... Yes No
35. Do you sometimes get out of breath just sitting still? ..... Yes No
36. Are your ankles often badly swollen? ..... Yes No
37. Do cold hands or feet trouble you even in hot weather? ..... Yes No
38. Do you suffer from frequent cramps in your legs? ..... Yes No
39. Has a doctor ever said you had heart trouble? Yes No
40. Does heart trouble run in your family? ..... Yes No

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**D**

41. Have you lost more than half your teeth? ..... Yes No
42. Are you troubled by bleeding gums? ..... Yes No
43. Have you often had severe toothaches? ..... Yes No
44. Is your tongue usually badly coated? ..... Yes No
45. Is your appetite always poor? ..... Yes No
46. Do you usually eat sweets or other food between meals? ..... Yes No
47. Do you always gulp your food in a hurry? ... Yes No
48. Do you often suffer from an upset stomach? Yes No
49. Do you usually feel bloated after eating? ..... Yes No
50. Do you usually belch a lot after eating? ..... Yes No
51. Are you often sick to your stomach? ..... Yes No
52. Do you suffer from indigestion? ..... Yes No
53. Do severe pains in the stomach often double you up? ..... Yes No
54. Do you suffer from constant stomach trouble? Yes No
55. Does stomach trouble run in your family? ... Yes No
56. Has a doctor ever said you had stomach ulcers? ..... Yes No
57. Do you suffer from frequent loose bowel movements? ..... Yes No
58. Have you ever had severe bloody diarrhea? ... Yes No
59. Were you ever troubled with intestinal worms? ..... Yes No
60. Do you constantly suffer from bad constipation? ..... Yes No
61. Have you ever had piles (rectal hemorrhoids)? ..... Yes No
62. Have you ever had jaundice (yellow eyes and skin)? ..... Yes No
63. Have you ever had serious liver or gall bladder trouble? ..... Yes No

**E**

64. Are your joints often painfully swollen? ..... Yes No
65. Do your muscles and joints constantly feel stiff? ..... Yes No
66. Do you usually have severe pains in the arms or legs? ..... Yes No
67. Are you crippled with severe rheumatism (arthritis)? ..... Yes No
68. Does rheumatism (arthritis) run in your family? ..... Yes No
69. Do weak or painful feet make your life miserable? ..... Yes No
70. Do pains in the back make it hard for you to keep up with your work? ..... Yes No
71. Are you troubled with a serious bodily disability or deformity? ..... Yes No

**F**

72. Is your skin very sensitive or tender? ..... Yes No
73. Do cuts in your skin usually stay open a long time? ..... Yes No
74. Does your face often get badly flushed? ..... Yes No
75. Do you sweat a great deal even in cold weather? ..... Yes No
76. Are you often bothered by severe itching? ... Yes No
77. Does your skin often break out in a rash? ..... Yes No
78. Are you often troubled with boils? ..... Yes No

**G**

79. Do you suffer badly from frequent severe headaches? ..... Yes No
80. Does pressure or pain in the head often make life miserable? ..... Yes No
81. Are headaches common in your family? ..... Yes No
82. Do you have hot or cold spells? ..... Yes No
83. Do you often have spells of severe dizziness? Yes No
84. Do you frequently feel faint? ..... Yes No
85. Have you fainted more than twice in your life? ..... Yes No
86. Do you have constant numbness or tingling in any part of your body? ..... Yes No
87. Was any part of your body ever paralyzed? Yes No
88. Were you ever knocked unconscious? ..... Yes No
89. Have you at times had a twitching of the face, head or shoulders? ..... Yes No
90. Did you ever have a fit or convulsion (epilepsy)? ..... Yes No
91. Has anyone in your family ever had fits or convulsions (epilepsy)? ..... Yes No
92. Do you bite your nails badly? ..... Yes No
93. Are you troubled by stuttering or stammering? ..... Yes No
94. Are you a sleep walker? ..... Yes No
95. Are you a bed wetter? ..... Yes No
96. Were you a bed wetter between the ages of 8 and 14? ..... Yes No

**GO TO NEXT PAGE**

**H**

97. Have you ever had anything seriously wrong with your genitals (privates)? ..... Yes No

98. Are your genitals often painful or sore? ..... Yes No

99. Have you ever had treatment for your genitals? ..... Yes No

100. Has a doctor ever said you had a hernia (rupture)? ..... Yes No

101. Have you ever passed blood while urinating (passing water)? ..... Yes No

102. Do you have trouble starting your stream when urinating? ..... Yes No

103. Do you have to get up every night and urinate? ..... Yes No

104. During the day, do you usually have to urinate frequently? ..... Yes No

105. Do you often have severe burning pain when you urinate? ..... Yes No

106. Do you sometimes lose control of your bladder? ..... Yes No

107. Has a doctor ever said you had kidney or bladder disease? ..... Yes No

**I**

108. Do you often get spells of complete exhaustion or fatigue? ..... Yes No

109. Does working tire you out completely? ..... Yes No

110. Do you usually get up tired and exhausted in the morning? ..... Yes No

111. Does every little effort wear you out? ..... Yes No

112. Are you constantly too tired and exhausted even to eat? ..... Yes No

113. Do you suffer from severe nervous exhaustion? ..... Yes No

114. Does nervous exhaustion run in your family? Yes No

**J**

115. Are you frequently ill? ..... Yes No

116. Are you frequently confined to bed by illness? ..... Yes No

117. Are you always in poor health? ..... Yes No

118. Are you considered a sickly person? ..... Yes No

119. Do you come from a sickly family? ..... Yes No

120. Do severe pains and aches make it impossible for you to do your work? ..... Yes No

121. Do you wear yourself out worrying about your health? ..... Yes No

122. Are you always ill and unhappy? ..... Yes No

123. Are you constantly made miserable by poor health? ..... Yes No

**K**

124. Did you ever have scarlet fever? ..... Yes No

125. As a child, did you have rheumatic fever, growing pains or twitching of the limbs? Yes No

126. Did you ever have malaria? ..... Yes No

127. Were you ever treated for severe anemia (thin blood)? ..... Yes No

128. Were you ever treated for "bad blood" (venereal disease)? ..... Yes No

129. Do you have diabetes (sugar disease)? ..... Yes No

130. Did a doctor ever say you had a goiter (in your neck)? ..... Yes No

131. Did a doctor ever treat you for tumor or cancer? ..... Yes No

132. Do you suffer from any chronic disease? ..... Yes No

133. Are you definitely *under* weight? ..... Yes No

134. Are you definitely *over* weight? ..... Yes No

135. Did a doctor ever say you had varicose veins (swollen veins) in your legs? ..... Yes No

136. Did you ever have a serious operation? ..... Yes No

137. Did you ever have a serious injury? ..... Yes No

138. Do you often have small accidents or injuries? ..... Yes No

**L**

139. Do you usually have great difficulty in falling asleep or staying asleep? ..... Yes No

140. Do you find it impossible to take a regular rest period each day? ..... Yes No

141. Do you find it impossible to take regular daily exercise? ..... Yes No

142. Do you smoke more than 20 cigarettes a day? ..... Yes No

143. Do you drink more than six cups of coffee or tea a day? ..... Yes No

144. Do you usually take two or more alcoholic drinks a day? ..... Yes No

**TURN TO NEXT PAGE**

**M**

145. Do you sweat or tremble a lot during examinations or questioning? Yes No

146. Do you get nervous and shaky when approached by a superior? Yes No

147. Does your work fall to pieces when the boss or a superior is watching you? Yes No

148. Does your thinking get completely mixed up when you have to do things quickly? Yes No

149. Must you do things very slowly in order to do them without mistakes? Yes No

150. Do you always get directions and orders wrong? Yes No

151. Do strange people or places make you afraid? Yes No

152. Are you scared to be alone when there are no friends near you? Yes No

153. Is it always hard for you to make up your mind? Yes No

154. Do you wish you always had someone at your side to advise you? Yes No

155. Are you considered a clumsy person? Yes No

156. Does it bother you to eat anywhere except in your own home? Yes No

**N**

157. Do you feel alone and sad at a party? Yes No

158. Do you usually feel unhappy and depressed? Yes No

159. Do you often cry? Yes No

160. Are you always miserable and blue? Yes No

161. Does life look entirely hopeless? Yes No

162. Do you often wish you were dead and away from it all? Yes No

**O**

163. Does worrying continually get you down? Yes No

164. Does worrying run in your family? Yes No

165. Does every little thing get on your nerves and wear you out? Yes No

166. Are you considered a nervous person? Yes No

167. Does nervousness run in your family? Yes No

168. Did you ever have a nervous breakdown? Yes No

169. Did anyone in your family ever have a nervous breakdown? Yes No

170. Were you ever a patient in a *mental* hospital (for your nerves)? Yes No

171. Was anyone in your family ever a patient in a *mental* hospital (for their nerves)? Yes No

**P**

172. Are you extremely shy or sensitive? Yes No

173. Do you come from a shy or sensitive family? Yes No

174. Are your feelings easily hurt? Yes No

175. Does criticism always upset you? Yes No

176. Are you considered a touchy person? Yes No

177. Do people usually misunderstand you? Yes No

**Q**

178. Do you have to be on your guard even with friends? Yes No

179. Do you always do things on sudden impulse? Yes No

180. Are you easily upset or irritated? Yes No

181. Do you go to pieces if you don't constantly control yourself? Yes No

182. Do little annoyances get on your nerves and make you angry? Yes No

183. Does it make you angry to have anyone tell you what to do? Yes No

184. Do people often annoy and irritate you? Yes No

185. Do you flare up in anger if you can't have what you want right away? Yes No

186. Do you often get into a violent rage? Yes No

**R**

187. Do you often shake or tremble? Yes No

188. Are you constantly keyed up and jittery? Yes No

189. Do sudden noises make you jump or shake badly? Yes No

190. Do you tremble or feel weak whenever someone shouts at you? Yes No

191. Do you become scared at sudden movements or noises at night? Yes No

192. Are you often awakened out of your sleep by frightening dreams? Yes No

193. Do frightening thoughts keep coming back in your mind? Yes No

194. Do you often become suddenly scared for no good reason? Yes No

195. Do you often break out in a cold sweat? Yes No

History Number_____

(WOMEN)

## CORNELL MEDICAL INDEX

# HEALTH QUESTIONNAIRE

Date_____

Print Your Name_____ Your Home Address_____

How Old Are You?_____ Circle If You Are . . Single, Married, Widowed, Separated, Divorced.

Circle the Highest Year You Reached In School | 1 2 3 4 5 6 7 8 | Elementary School | 1 2 3 4 | High | 1 2 3 4 | College

What Is Your Occupation?_____

**Directions:** This questionnaire is for ***WOMEN ONLY.***
If you can answer **YES** to the question asked, put a circle around the (Yes)
If you have to answer **NO** to the question asked, put a circle around the (No)
Answer all questions. If you are not sure, guess.

**A**

1. Do you need glasses to read? ..... Yes No
2. Do you need glasses to see things at a distance? ..... Yes No
3. Has your eyesight often blacked out completely? ..... Yes No
4. Do your eyes continually blink or water? ..... Yes No
5. Do you often have bad pains in your eyes? ... Yes No
6. Are your eyes often red or inflamed? ..... Yes No
7. Are you hard of hearing? ..... Yes No
8. Have you ever had a bad running ear? ..... Yes No
9. Do you have constant noises in your ears? ..... Yes No

**B**

10. Do you have to clear your throat frequently? Yes No
11. Do you often feel a choking lump in your throat? ..... Yes No
12. Are you often troubled with bad spells of sneezing? ..... Yes No
13. Is your nose continually stuffed up? ..... Yes No
14. Do you suffer from a constantly running nose? ..... Yes No
15. Have you at times had bad nose bleeds? ..... Yes No
16. Do you often catch severe colds? ..... Yes No
17. Do you frequently suffer from heavy chest colds? ..... Yes No
18. When you catch a cold, do you always have to go to bed? ..... Yes No
19. Do frequent colds keep you miserable all winter? ..... Yes No
20. Do you get hay fever? ..... Yes No
21. Do you suffer from asthma? ..... Yes No
22. Are you troubled by constant coughing? ..... Yes No
23. Have you ever coughed up blood? ..... Yes No
24. Do you sometimes have severe soaking sweats at night? ..... Yes No
25. Have you ever had a chronic chest condition? Yes No
26. Have you ever had T.B. (Tuberculosis)? ..... Yes No
27. Did you ever live with anyone who had T.B.? Yes No

**C**

28. Has a doctor ever said your blood pressure was too *high?* ..... Yes No
29. Has a doctor ever said your blood pressure was too *low?* ..... Yes No
30. Do you have pains in the heart or chest? ..... Yes No
31. Are you often bothered by thumping of the heart? ..... Yes No
32. Does your heart often race like mad? ..... Yes No
33. Do you often have difficulty in breathing? ... Yes No
34. Do you get out of breath long before anyone else? ..... Yes No
35. Do you sometimes get out of breath just sitting still? ..... Yes No
36. Are your ankles often badly swollen? ..... Yes No
37. Do cold hands or feet trouble you even in hot weather? ..... Yes No
38. Do you suffer from frequent cramps in your legs? ..... Yes No
39. Has a doctor ever said you had heart trouble? Yes No
40. Does heart trouble run in your family? ..... Yes No

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**D**

41. Have you lost more than half your teeth? ..... Yes No
42. Are you troubled by bleeding gums? ..... Yes No
43. Have you often had severe toothaches? ..... Yes No
44. Is your tongue usually badly coated? ..... Yes No
45. Is your appetite always poor? ..... Yes No
46. Do you usually eat sweets or other food between meals? ..... Yes No
47. Do you always gulp your food in a hurry? ... Yes No
48. Do you often suffer from an upset stomach? Yes No
49. Do you usually feel bloated after eating? ..... Yes No
50. Do you usually belch a lot after eating? ..... Yes No
51. Are you often sick to your stomach? ..... Yes No
52. Do you suffer from indigestion? ..... Yes No
53. Do severe pains in the stomach often double you up? ..... Yes No
54. Do you suffer from constant stomach trouble? Yes No
55. Does stomach trouble run in your family? ... Yes No
56. Has a doctor ever said you had stomach ulcers? ..... Yes No
57. Do you suffer from frequent loose bowel movements? ..... Yes No
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59. Were you ever troubled with intestinal worms? ..... Yes No
60. Do you constantly suffer from bad constipation? ..... Yes No
61. Have you ever had piles (rectal hemorrhoids)? ..... Yes No
62. Have you ever had jaundice (yellow eyes and skin)? ..... Yes No
63. Have you ever had serious liver or gall bladder trouble? ..... Yes No

**E**

64. Are your joints often painfully swollen? ..... Yes No
65. Do your muscles and joints constantly feel stiff? ..... Yes No
66. Do you usually have severe pains in the arms or legs? ..... Yes No
67. Are you crippled with severe rheumatism (arthritis)? ..... Yes No
68. Does rheumatism (arthritis) run in your family? ..... Yes No
69. Do weak or painful feet make your life miserable? ..... Yes No
70. Do pains in the back make it hard for you to keep up with your work? ..... Yes N
71. Are you troubled with a serious bodily disability or deformity? ..... Yes N

**F**

72. Is your skin very sensitive or tender? ..... Yes N
73. Do cuts in your skin usually stay open a long time? ..... Yes N
74. Does your face often get badly flushed? ..... Yes N
75. Do you sweat a great deal even in cold weather? ..... Yes N
76. Are you often bothered by severe itching? ... Yes N
77. Does your skin often break out in a rash? ..... Yes N
78. Are you often troubled with boils? ..... Yes N

**G**

79. Do you suffer badly from frequent severe headaches? ..... Yes No
80. Does pressure or pain in the head often make life miserable? ..... Yes No
81. Are headaches common in your family? ..... Yes No
82. Do you have hot or cold spells? ..... Yes No
83. Do you often have spells of severe dizziness? Yes No
84. Do you frequently feel faint? ..... Yes No
85. Have you fainted more than twice in your life? ..... Yes No
86. Do you have constant numbness or tingling in any part of your body? ..... Yes No
87. Was any part of your body ever paralyzed? Yes No
88. Were you ever knocked unconscious? ..... Yes No
89. Have you at times had a twitching of the face, head or shoulders? ..... Yes No
90. Did you ever have a fit or convulsion (epilepsy)? ..... Yes No
91. Has anyone in your family ever had fits or convulsions (epilepsy)? ..... Yes No
92. Do you bite your nails badly? ..... Yes No
93. Are you troubled by stuttering or stammering? ..... Yes No
94. Are you a sleep walker? ..... Yes No
95. Are you a bed wetter? ..... Yes No
96. Were you a bed wetter between the ages of 8 and 14? ..... Yes No

**GO TO NEXT PAGE**

**H**

97. Have your menstrual periods usually been painful? ..... Yes No
98. Have you often felt weak or sick with your periods? ..... Yes No
99. Have you often had to lie down when your periods came on? ..... Yes No
100. Have you usually been tense or jumpy with your periods? ..... Yes No
101. Have you ever had constant severe hot flashes and sweats? ..... Yes No
102. Have you often been troubled with a vaginal discharge? ..... Yes No
103. Do you have to get up every night and urinate? ..... Yes No
104. During the day, do you usually have to urinate frequently? ..... Yes No
105. Do you often have severe burning pain when you urinate? ..... Yes No
106. Do you sometimes lose control of your bladder? ..... Yes No
107. Has a doctor ever said you had kidney or bladder disease? ..... Yes No

**I**

108. Do you often get spells of complete exhaustion or fatigue? ..... Yes No
109. Does working tire you out completely? ..... Yes No
110. Do you usually get up tired and exhausted in the morning? ..... Yes No
111. Does every little effort wear you out? ..... Yes No
112. Are you constantly too tired and exhausted even to eat? ..... Yes No
113. Do you suffer from severe nervous exhaustion? ..... Yes No
114. Does nervous exhaustion run in your family? Yes No

**J**

115. Are you frequently ill? ..... Yes No
116. Are you frequently confined to bed by illness? ..... Yes No
117. Are you always in poor health? ..... Yes No
118. Are you considered a sickly person? ..... Yes No
119. Do you come from a sickly family? ..... Yes No
120. Do severe pains and aches make it impossible for you to do your work? ..... Yes No
121. Do you wear yourself out worrying about your health? ..... Yes No
122. Are you always ill and unhappy? ..... Yes No
123. Are you constantly made miserable by poor health? ..... Yes No

**K**

124. Did you ever have scarlet fever? ..... Yes No
125. As a child, did you have rheumatic fever, growing pains or twitching of the limbs? Yes No
126. Did you ever have malaria? ..... Yes No
127. Were you ever treated for severe anemia (thin blood)? ..... Yes No
128. Were you ever treated for "bad blood" (venereal disease)? ..... Yes No
129. Do you have diabetes (sugar disease)? ..... Yes No
130. Did a doctor ever say you had a goiter (in your neck)? ..... Yes No
131. Did a doctor ever treat you for tumor or cancer? ..... Yes No
132. Do you suffer from any chronic disease? ..... Yes No
133. Are you definitely *under* weight? ..... Yes No
134. Are you definitely *over* weight? ..... Yes No
135. Did a doctor ever say you had varicose veins (swollen veins) in your legs? ..... Yes No
136. Did you ever have a serious operation? ..... Yes No
137. Did you ever have a serious injury? ..... Yes No
138. Do you often have small accidents or injuries? ..... Yes No

**L**

139. Do you usually have great difficulty in falling asleep or staying asleep? ..... Yes No
140. Do you find it impossible to take a regular rest period each day? ..... Yes No
141. Do you find it impossible to take regular daily exercise? ..... Yes No
142. Do you smoke more than 20 cigarettes a day? ..... Yes No
143. Do you drink more than six cups of coffee or tea a day? ..... Yes No
144. Do you usually take two or more alcoholic drinks a day? ..... Yes No

**TURN TO NEXT PAGE**

**M**

145. Do you sweat or tremble a lot during examinations or questioning? Yes No

146. Do you get nervous and shaky when approached by a superior? Yes No

147. Does your work fall to pieces when the boss or a superior is watching you? Yes No

148. Does your thinking get completely mixed up when you have to do things quickly? Yes No

149. Must you do things very slowly in order to do them without mistakes? Yes No

150. Do you always get directions and orders wrong? Yes No

151. Do strange people or places make you afraid? Yes No

152. Are you scared to be alone when there are no friends near you? Yes No

153. Is it always hard for you to make up your mind? Yes No

154. Do you wish you always had someone at your side to advise you? Yes No

155. Are you considered a clumsy person? Yes No

156. Does it bother you to eat anywhere except in your own home? Yes No

**N**

157. Do you feel alone and sad at a party? Yes No

158. Do you usually feel unhappy and depressed? Yes No

159. Do you often cry? Yes No

160. Are you always miserable and blue? Yes No

161. Does life look entirely hopeless? Yes No

162. Do you often wish you were dead and away from it all? Yes No

**O**

163. Does worrying continually get you down? Yes No

164. Does worrying run in your family? Yes No

165. Does every little thing get on your nerves and wear you out? Yes No

166. Are you considered a nervous person? Yes No

167. Does nervousness run in your family? Yes No

168. Did you ever have a nervous breakdown? Yes No

169. Did anyone in your family ever have a nervous breakdown? Yes No

170. Were you ever a patient in a *mental* hospital (for your nerves)? Yes No

171. Was anyone in your family ever a patient in a *mental* hospital (for their nerves)? Yes No

**P**

172. Are you extremely shy or sensitive? Yes No

173. Do you come from a shy or sensitive family? Yes No

174. Are your feelings easily hurt? Yes No

175. Does criticism always upset you? Yes No

176. Are you considered a touchy person? Yes No

177. Do people usually misunderstand you? Yes No

**Q**

178. Do you have to be on your guard even with friends? Yes No

179. Do you always do things on sudden impulse? Yes No

180. Are you easily upset or irritated? Yes No

181. Do you go to pieces if you don't constantly control yourself? Yes No

182. Do little annoyances get on your nerves and make you angry? Yes No

183. Does it make you angry to have anyone tell you what to do? Yes No

184. Do people often annoy and irritate you? Yes No

185. Do you flare up in anger if you can't have what you want right away? Yes No

186. Do you often get into a violent rage? Yes No

**R**

187. Do you often shake or tremble? Yes No

188. Are you constantly keyed up and jittery? Yes No

189. Do sudden noises make you jump or shake badly? Yes No

190. Do you tremble or feel weak whenever someone shouts at you? Yes No

191. Do you become scared at sudden movements or noises at night? Yes No

192. Are you often awakened out of your sleep by frightening dreams? Yes No

193. Do frightening thoughts keep coming back in your mind? Yes No

194. Do you often become suddenly scared for no good reason? Yes No

195. Do you often break out in a cold sweat? Yes No

# THE TAYLOR MANIFEST ANXIETY SCALE

**Instructions:** Please fill in this form by putting a circle around the 'True' or 'False' following each statement. If you find it difficult to decide, ask yourself whether you think the statement is on the whole true or false and put a circle round the appropriate word.

REMEMBER TO ANSWER EACH STATEMENT

| | | | |
|---|---|---|---|
| 1. | My sleep is fitful and disturbed ..... | True | False |
| 2. | I have had periods in which I lost sleep over worry ..... | True | False |
| 3. | I have very few fears compared with my friends ..... | True | False |
| 4. | I believe I am no more nervous than most others ..... | True | False |
| 5. | I have nightmares every few nights ..... | True | False |
| 6. | I have had a great deal of stomach trouble ..... | True | False |
| 7. | I frequently notice my hands shake when I try to do something ..... | True | False |
| 8. | I suffer from attacks of diarrhoea ..... | True | False |
| 9. | I worry over money and business ..... | True | False |
| 10. | I am troubled by attacks of nausea ..... | True | False |
| 11. | I am often afraid that I am going to blush ..... | True | False |
| 12. | I feel hungry almost all the time ..... | True | False |
| 13. | I am entirely self-confident ..... | True | False |
| 14. | I do not tire quickly ..... | True | False |
| 15. | It makes me nervous to have to wait ..... | True | False |
| 16. | Sometimes I become so excited that I find it hard to get to sleep .. | True | False |
| 17. | I am usually calm and not easily upset ..... | True | False |
| 18. | I have periods of such great restlessness that I cannot sit long in a chair ..... | True | False |
| 19. | I am happy most of the time ..... | True | False |
| 20. | I find it hard to keep my mind on a task or job ..... | True | False |
| 21. | I feel anxiety about something or someone almost all the time ..... | True | False |
| 22. | I shrink from facing a crisis or difficulty ..... | True | False |
| 23. | I wish I could be as happy as others seem to be ..... | True | False |
| 24. | I frequently find myself worrying about something ..... | True | False |
| 25. | I certainly feel useless at times ..... | True | False |
| 26. | I sometimes feel that I am about to go to pieces ..... | True | False |
| 27. | I sweat very easily even on cool days ..... | True | False |

28. /

| | | | |
|---|---|---|---|
| 28. | Life is a strain for me much of the time ..... | True | False |
| 29. | I worry over possible misfortune ..... | True | False |
| 30. | I am unusually self-conscious ..... | True | False |
| 31. | I hardly ever notice my heart pounding and I am seldom short of breath ..... | True | False |
| 32. | I cry easily ..... | True | False |
| 33. | I have been afraid of things or people that I know could not hurt me ..... | True | False |
| 34. | I am inclined to take things hard ..... | True | False |
| 35. | I have very few headaches ..... | True | False |
| 36. | I must admit that I have at times been worried beyond reason over something that really did not matter ..... | True | False |
| 37. | I cannot keep my mind on one thing ..... | True | False |
| 38. | I am easily embarassed ..... | True | False |
| 39. | At times I think I am no good at all ..... | True | False |
| 40. | I am a highly strung person ..... | True | False |
| 41. | Sometimes when embarrassed, I break out in a sweat which annoys me greatly ..... | True | False |
| 42. | I blush no more often than others ..... | True | False |
| 43. | I am more sensitive than most other people ..... | True | False |
| 44. | I practically never blush ..... | True | False |
| 45. | I have sometimes felt that difficulties were piling up so high that I could not overcome them ..... | True | False |
| 46. | I work under a great deal of tension ..... | True | False |
| 47. | My hands and feet are usually warm enough ..... | True | False |
| 48. | I dream frequently about things that are best kept to myself .... | True | False |
| 49. | I lack self-confidence ..... | True | False |
| 50. | I am very seldom troubled by constipation ..... | True | False |

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