of the 70–79 age group. The frequency was higher in women than in men for all ages, though the differences were very small in the 80–89 group. At ages below 50 gall-stones were more frequent in married women without children than in single women, and more frequent in married women with children than in married nulliparae. Beyond the age of 49 the related incidence was higher in married nulliparae than in married women with children.

It was argued that by combining data from clinical and post-mortem material a more accurate description of the distribution of gall-stones in the living population could be obtained than from consideration of either set of data alone. It was found that gall-stones increase in frequency with age, but that in females after the sixth decade and males after the eighth there is a high proportion of "silent" stones.

It is concluded that, in women, age changes in the incidence of cholelithiasis are modified by factors operating in and related to the child-bearing period.

In the years following the female climacteric, sex differences in the incidence of cholelithiasis appear to diminish until there are virtually no differences in the oldest age group.

At ages under 50, women with gall-stones were heavier than normal women of a comparable age and height. After 50, differences in weight were no longer apparent.

Analysis of stones found at necropsy showed the mixed type to be most frequent, the pigment type next, and the cholesterol type least frequent in both sexes.

Comparisons were drawn between the incidence of gall-stones and of atherosclerosis. Prior to the menopause there is a sex difference in cholesterol metabolism. It is suggested that this difference is expressed in women by a high frequency of cholelithiasis and a low frequency of atherosclerosis, whilst the reverse occurs in men. After the menopause, when hormonal differences between the two sexes become less clearly defined, the pathways of cholesterol metabolism may converge and so account for the diminishing sex differences in the related incidence of gall-stones and atherosclerosis among the older age groups.

My thanks are due to Professor Lancelot Hogben, F.R.S., Dr. R. G. Record, and Dr. R. H. Cawley for their interest in this work; to Dr. Wallis Taylor for his assistance with the statistical analysis of the data; and to Professor J. W. Orr for allowing access to the post-mortem records.

REFERENCES

Andrews, E., Schoenheimer, R., and Hrdina, L. (1932). *Arch. Surg. (Chicago)*, **25**, 796.
Cappell, D. F. (1951). *Muir's Textbook of Pathology*, p. 672. Arnold, London.
Census, 1951. Great Britain One per cent. Sample Tables, Parts I and II. (1952). H.M.S.O., London.
Cleland, J. B. (1953). *Med. J. Aust.*, **2**, 488.
Engle, E. T. (1955). *Recent Progr. Hormone Res.*, **11**, 291.
Griffin, G. D. J., and Smith, L. A. (1954). *J. Amer. med. Ass.*, **154**, 731.
Gross, D. M. B. (1929). *J. Path. Bact.*, **32**, 503.
Jones, H. B., Gofman, J. W., Lindgren, F. T., Lyon, T. P., Graham, D. M., Strisower, B., and Nichols, A. V. (1951). *Amer. J. Med.*, **11**, 358.
Joske, R. A., Saint, E. G., Bromilow, F. J., and Hughes, E. S. R. (1954). *Med. J. Aust.*, **2**, 473.
Kemsley, W. F. F. (1950). *Ann. Eugen. (Camb.)*, **15**, 161.
Lowe, C. R., and Gibson, J. R. (1955). *British Medical Journal*, **2**, 1006.
Okey, R., and Boyden, R. E. (1927). *J. biol. Chem.*, **72**, 261.
Oliver, M. F., and Boyd, G. S. (1953). *Brit. Heart J.*, **15**, 387.
Pincus, G., Dorfman, R. I., Romanoff, L. P., Rubin, B. L., Bloch, E., Carlo, J., and Freeman H. (1955). *Recent Progr. Hormone Res.*, **11**, 307.
Report on the Family Census of 1946 (1954). H.M.S.O., London.
Robertson, H. E., and Dochat, G. R. (1944). *Int. Abstr. Surg.*, **78**, 193.
Stuermer, K. (1947). *Zbl. Gynäk.*, **69**, 460.

AETIOLOGY OF GRAVES'S DISEASE IN RELATION TO RECENT EXPERIMENTAL FINDINGS

BY

G. W. HARRIS, M.D., Sc.D., F.R.S.

AND

J. W. WOODS, Ph.D.

Department of Neuroendocrinology, Institute of Psychiatry, British Postgraduate Medical Federation, Maudsley Hospital, London

Emotional Trauma and Graves's Disease

The occurrence of hyperthyroidism following a severe fright was first reported by Parry in 1825, when he described the condition that was later to be called Graves's disease. Ever since this first account innumerable papers describing the condition have confirmed the frequency with which emotional or psychological upsets precede the onset of thyrotoxicosis. The French school of Charcot (1859), Trousseau (1867), and others believed the disease to be nervous in origin, either a form of hysteria or associated with a definite but undetermined lesion. Such further publications as those of Crawford (1897), Marañón (1921), Deutsch (1923), Lewis (1925), Bram (1927), Moschcowitz (1930), Goodall and Rogers (1933), and many others afford evidence of the relation between psychic trauma and the onset of the hyperthyroid state.

More recent work has been devoted to the type of individual and type of disturbance likely to be associated with thyrotoxicosis. Lidz and Whitehorn (1950) have described the type of patient in whom Graves's disease occurs as one highly dependent on interpersonal relationships for his security. This relationship is often familial, such as that of a daughter to mother or a mother to child. There is little latitude for adaptability, and the patient feels abject and helpless without such symbiotic relationship. These patients react in a highly emotional or exaggerated fashion to the disruption, or threat of disruption, of such a relationship. It is this type of emotional stress which threatens their security that is apt to precipitate Graves's disease.

It has been stated that the incidence of Graves's disease declines in times of economic depression, and it is possible that such social conditions bind families into closer-knit units. On the other hand, however, it is clear that emotional stress does not result in Graves's disease in a high proportion of the population. The aerial bombardment of large towns and cities during the last war did not appear to increase the incidence of thyrotoxicosis, though in some Scandinavian countries subject to occupation thyrotoxicosis is said to have reached epidemic proportions (see discussion following the paper of Lidz and Whitehorn, 1950). If emotional stress is an aetiological factor of importance, as seems likely, it is not the sole factor underlying the onset of the disease.

In view of the possible relationship between the central nervous system and thyroid activity, it became of interest to see the effect of prolonged (one to seven days) electrical stimulation of the hypothalamus on thyroid activity.

Electrical Stimulation of Hypothalamus, Thyrotrophic Secretion by Anterior Pituitary Gland, and Thyroid Activity in the Normal Animal

Few reports in the literature describe the effects of electrical stimulation of the hypothalamus on the thyroid gland. Green and Harris (unpublished, quoted by Harris, 1955) saw no increase in the oxygen consumption of rabbits following prolonged stimulation of the hypothalamus, but drew no conclusions from these data owing to the limitations of the method for measuring metabolic rate in rabbits. Colfer (1949) observed histological signs of increased thyroid activity in rats and rabbits after four one-hour periods of hypothalamic stimulation on each of two days.

In a recent study Harris and Woods (unpublished) have employed the method of remote control (de Groot and Harris, 1950) of electrical stimulation as applied to various regions of the hypothalamus and pituitary gland, and the ^{131}I output method (Brown-Grant, von Euler, Harris, and Reichlin, 1954) for indicating changes in thyroid function. These techniques permit (*a*) electrical stimulation to be applied to the unanaesthetized and unrestrained animal for long periods (usually 48 hours), and (*b*) continuous observation of thyroid activity to be made over an interval of 10 to 14 days. Out of 35 experiments on 22 rabbits in which the electrode was situated in some part of the hypothalamus or pituitary gland, stimulation resulted in thyroid inhibition in 20, no change in thyroid activity in 14, and a questionable result in one case. In one further animal a definite increase in thyroid activity occurred on two occasions. Since thyroid acceleration was observed in only 2 out of 37 experiments it was felt possible that some other factor was inhibiting or masking the effects of an increased secretion of thyrotrophic hormone in these experiments. One possibility appeared to be that the secretion of the adrenocorticotrophic hormone and excitation of the adrenal cortex known to follow such hypothalamic stimulation prevented in some way the pituitary secretion of T.S.H.

Effect of Adrenal Steroids on Thyroid Activity

It is now well established that electrical stimulation of the tuber cinereum elicits increased discharge of corticotrophin from the anterior pituitary gland and a rise in the concentration of the adrenal cortical steroids in the blood (de Groot and Harris, 1950; Hume and Wittenstein, 1950; Porter, 1953, 1954). The effect of the injection of corticotrophin or adrenal steroids on thyroid activity has been studied by many workers using different criteria for assessing such activity. A depression of ^{131}I uptake by the thyroid gland has been found to follow administration of corticotrophin or cortisone to man (see Hill, Reiss, Forsham, and Thorn, 1950; Berson and Yalow, 1952; Kuhl and Ziff, 1952), rabbit (Myant, 1953), and rat (Money, Kraintz, Fager, Kirschner, and Rawson, 1951; Perry, 1951; Albert, Tenney, and Ford, 1952; Verzár and Vidovic, 1952; Migeon, Gardner, Crigler, and Wilkins, 1952). A similar depression of thyroid activity following the administration of corticotrophin and cortisone has been shown in the rat (Brown-Grant, 1955, 1956) and rabbit (Myant, 1953; Brown-Grant, Harris, and Reichlin, 1954; Brown-Grant, 1956) using the ^{131}I output method.

That the inhibition of the thyroid following the injection of corticotrophin is due to adrenal activation is shown by the fact that corticotrophin injection in cases of Addison's disease (Hill *et al.*, 1950) or into adrenalectomized rats (Brown-Grant, 1956) is without effect on thyroid function. It is also of interest that injection of both corticosterone and hydrocortisone (which are known to be secreted by the rabbit adrenal cortex) inhibit the release of radioactive hormone from the rabbit thyroid (Brown-Grant, 1956).

It is probable that the adrenal steroids affect thyroid activity by suppressing the secretion of thyrotrophic hormone from the anterior pituitary, since cortisone was found not to influence the response of the thyroid gland of the hypophysectomized rabbit to injection of T.S.H. (Brown-Grant, Harris, and Reichlin, 1954).

Electrical Stimulation of the Hypothalamus and Thyroid Activity in the Adrenalectomized Animal

In view of the above data the effect of electrical stimulation of the tuber cinereum on thyroid activity was investigated in adrenalectomized rabbits maintained on constant daily doses of cortisone. Fourteen such rabbits have been studied (Harris and Woods, unpublished), using the techniques mentioned above. Electrical stimulation evoked a marked and consistent increase in thyroid activity in 20 experiments on 10 animals (though previous to adrenalectomy these animals had shown thyroid inhibition in 10 experiments and no change in thyroid activity in five experiments). Ten experiments in the other four animals showed no observable change in thyroid function on eight occasions, an inhibition on one occasion, and a questionable result on one occasion. The precise location of the region stimulated in the various animals has not yet been determined by histological study, but the radiographic evidence suggests that it is stimulation of the median eminence of the tuber cinereum which results in increased thyroid activity.

During five experiments on four rabbits in which increased thyroid activity was observed from measurements of thyroidal radio-iodine, estimations of the plasma radioactivity revealed a marked increase (up to $\times 3\frac{1}{2}$) during the period of stimulation. It is significant that hypothalamic stimulation could maintain an increased level of thyroid activity even in the presence of a high concentration of thyroid hormone in the blood. Five out of the 10 rabbits that showed a marked acceleration of thyroid activity during stimulation eventually died, suddenly and unexpectedly, while being stimulated.

In view of the striking difference in the results obtained in normal and adrenalectomized animals, it is of interest to consider the data regarding adrenal cortical function in Graves's disease.

Adrenal Cortical Function in Graves's Disease

An important relationship between the adrenal cortex and Graves's disease has been suspected for many years. Boyd (1944) states: "The more carefully the matter is studied the more clearly does an underlying relationship become evident between three such apparently different conditions as exophthalmic goitre, status lymphaticus, and Addison's disease." In 1921 Marine and Baumann reported increased heat production, increased respiratory exchange, and a symptom-complex resembling exophthalmic goitre following removal or damage to the adrenal glands in rabbits. Marine (1930) pointed out that thyrotoxicosis in the human is often associated with signs of adrenal cortical underactivity (lymphoid hyperplasia and a large thymus) and a small adrenal cortex. LeCompte (1949) measured the width of the adrenal cortex in cases of Graves's disease and found a significant narrowing of the cortex in such cases. The onset of Graves's disease has been noted to follow *x*-ray damage to the adrenal cortex in the human (Oppenheimer, 1937), and the incidence of thyrotoxicosis has been reported to be ten times greater in patients suffering from Addison's disease than in normals (Frederickson, 1951).

The techniques developed for estimating adrenal cortical activity during life have shown that in hyperthyroidism the urinary excretion of 17-ketosteroids may be low (Fraser, Forbes, Albright, Sulkowitch, and Reifenstein, 1941; Shadaksharappa, Calloway, Kyle, and Keeton, 1951; Corvilain, 1953), the excretion of reducing steroids may be normal or slightly increased (Shadaksharappa *et al.*, 1951; Talbot, Wood, Worcester, Christo, Campbell, and Zygmuntowicz, 1951), and the urinary formaldehydogenic steroids are decreased (Daughaday, Jaffe, and Williams, 1948). In the study of Daughaday *et al.* (1948) serial studies of a patient showed that a severe exacerbation of the thyrotoxic state was accompanied by a fall in the excretion of formaldehydogenic steroids.

In a more recent study (Levin and Daughaday, 1955) the excretion of urinary 17-ketosteroids and 17-hydroxysteroids

was found to be within the normal range in hyperthyroidism. The surprising feature of these data is that urinary excretion of adrenal steroids is not greatly increased in Graves's disease, for the administration of exogenous thyroxine is known to result in adrenal hypertrophy (Wallach and Reineke, 1949; and others), an increased excretion of 17-hydroxysteroids in the guinea-pig (Levin and Daughaday, 1955), and an increased excretion of 17-ketosteroids in man (Corvilain, 1953). Also the emotional and physical state of a patient with thyrotoxicosis would appear to afford a strong stimulus for adrenal cortical hyperactivity. It is probable, then, that there is a relative, if not an absolute, degree of adrenal cortical hypoactivity in this condition.

General Conclusions

A comparison may be drawn between (1) the findings of Harris and Woods (unpublished) that electrical stimulation of the tuber cinereum of the hypothalamus in the normal rabbit results in inhibition of, or no change in, thyroid activity (rarely thyroid acceleration), whereas the identical procedure in the same animals after adrenalectomy results in a consistent and marked increase in thyroid function; and (2) the clinical observations relating emotional stress and relative adrenal insufficiency with the state of thyrotoxicosis.

In a patient with Graves's disease it is possible that some stressful stimulus has resulted in decreased adrenocortical activity and increased thyroid activity. Such a response would seem to be the reverse of that which occurs in the normal individual. In support of this view is the clinical evidence of Hill *et al.* (1950) that corticotrophin administration may induce remission in early cases of thyrotoxicosis.

Summary

It has been found that electrical stimulation of the hypothalamus rarely elicits increased secretion of thyrotrophic hormone in rabbits with intact adrenal glands. Prior to adrenalectomy increased thyroid activity was observed in only one rabbit out of 22 during electrical stimulation of the hypothalamus. In 35 experiments on 21 such rabbits thyroid activity was either unchanged or actually decreased.

After bilateral adrenalectomy, performed on 14 of the 22 rabbits, hypothalamic stimulation consistently elicited a marked increase in thyroid activity in 20 experiments on 10 rabbits.

Thyroid activity was estimated by measuring the rate of release of ^{131}I from the thyroid and the blood concentration of P.B.^{131}I. Electrical stimulation of the brain was carried out in unanaesthetized and unrestrained rabbits by the remote control method.

These results seem to be of interest with respect to the aetiology of Graves's disease, since: (1) there is a probable relationship between psychological trauma and the onset or exacerbation of the state of hyperthyroidism; and (2) numerous clinical reports suggest that either a relative or an absolute adrenal insufficiency is a concomitant of Graves's disease.

It is felt that investigation of the effects of corticotrophin administration in early, previously untreated cases of Graves's disease would be of interest.

References

Albert, A., Tenney, A., and Ford, E. (1952). *Endocrinology*, **50**, 324.
Berson, S. A., and Yalow, R. S. (1952). *J. clin. Endocr.*, **12**, 407.
Boyd, W. (1944). *The Pathology of Internal Disease*, 4th ed. Kimpton, London.
Bram, I. (1927). *Endocrinology*, **11**, 106.
Brown-Grant, K. (1955). Ibid., **56**, 607.
—— (1956). *J. Physiol. (Lond.)*, **131**, 58.
—— von Euler, C., Harris, G. W., and Reichlin, S. (1954). Ibid., **126**, 1.
—— Harris, G. W., and Reichlin, S. (1954). Ibid., **126**, 41.
Charcot, J. M. (1859). *Gaz. hebd. Méd. Chir.*, **6**, 216.
Colfer, H. F. (1949). *Trans. Amer. Goiter Ass.*, p. 376.
Corvilain, J. (1953). *British Medical Journal*, **2**, 915.
Crawford, R. (1897). *King's Coll. Hosp. Rep.*, **3**, 45.
Daughaday, W. M., Jaffe, H., and Williams, R. H. (1948). *J. clin. Endocr.*, **8**, 244.
de Groot, J., and Harris, G. W. (1950). *J. Physiol. (Lond.)*, **111**, 335.
Deutsch, F. (1923). *Med. Klin.*, **19**, 678.
Fraser, R. W., Forbes, A. P., Albright, F., Sulkowitch, H., and Reifenstein, E. C., jun. (1941). *J. clin. Endocr.*, **1**, 234.
Frederickson, D. S. (1951). Ibid., **11**, 760.
Goodall, J. S., and Rogers, L. (1933). *Med. J. Rec.*, **138**, 411.
Harris, G. W. (1955). *Neural Control of the Pituitary Gland*. Arnold, London.
Hill, S. R., Reiss, R. S., Forsham, P. H., and Thorn, G. W. (1950). *J. clin. Endocr.*, **10**, 1375.
Hume, D. M., and Wittenstein, G. J. (1950). *Proc. 1st Clin. ACTH Conf.*, p. 134. Blakiston, Philadelphia.
Kuhl, W. J., and Ziff, M. (1952). *J. clin. Endocr.*, **12**, 554.
LeCompte, P. M. (1949). Ibid., **9**, 158.
Levin, M. E., and Daughaday, W. M. (1955). Ibid., **15**, 1499.
Lewis, Nolan D. C. (1925). *Med. J. Rec.*, **122**, 121.
Lidz, T., and Whitehorn, J. C. (1950). *Res. Publ. Ass. nerv. ment. Dis.*, **29**, 445.
Marañón, G. (1921). *Ann. Méd.*, **9**, 81.
Marine, D. (1930). *Amer. J. med. Sci.*, **180**, 767.
—— and Baumann, E. J. (1921). *Amer. J. Physiol.*, **57**, 135.
Migeon, C. J., Gardner, L. I., Crigler, J. F., jun., and Wilkins, L. (1952). *Endocrinology*, **51**, 117.
Money, W. L., Kraintz, L., Fager, J., Kirschner, L., and Rawson, R. W. (1951). Ibid., **48**, 682.
Moschcowitz, E. (1930). *Arch. intern. Med.*, **46**, 610.
Myant, N. B. (1953). *J. Physiol. (Lond.)*, **120**, 288.
Oppenheimer, B. S. (1937). *J. Mt Sinai Hosp.*, **4**, 214.
Parry, C. H. (1825). *Elements of Pathology and Therapeutics*, **2**, 111.
Perry, W. F. (1951). *Endocrinology*, **49**, 284.
Porter, R. W. (1953). *Amer. J. Physiol.*, **172**, 515.
—— (1954). *Rec. Progr. Hormone Res.*, **10**, 1.
Shadaksharappa, K., Calloway, N. O., Kyle, R. H., and Keeton, R. W. (1951). *J. clin. Endocr.*, **11**, 1383.
Talbot, N. B., Wood, M. S., Worcester, J., Christo, E., Campbell, A. M., and Zygmuntowicz, A. S. (1951). Ibid., **11**, 1224.
Trousseau, A. (1867). *Lectures on Clinical Medicine*, Translated by P. Victor Bazire and Sir John Rose Cormack, p. 542. New Sydenham Society, London.
Verzár, F., and Vidovic, V. (1952). *J. Endocr.*, **8**, 321.
Wallach, D. P., and Reineke, E. P. (1949). *Endocrinology*, **45**, 75.

PREFRONTAL LEUCOTOMY

VIEWS OF PATIENTS AND THEIR RELATIVES

BY

ALICK ELITHORN, M.D., M.R.C.P., D.P.M.

AND

ELIOT SLATER M.D., F.R.C.P., D.P.M.

From the Department of Psychological Medicine and the Neurological Research Unit of the Medical Research Council, the National Hospital for Nervous Diseases, Queen Square, London

Recent correspondence in the *Lancet* and the *British Medical Journal* has shown that there are still widely diverging views on the value of leucotomy in the treatment of mental disorders. Critics object either that the deleterious effects of the operation are insufficiently appreciated and outweigh trivial symptomatic improvements if such occur, or that if beneficial results are obtained then they are in some ill-specified way not ethically justifiable. Thus it has been stated that all the surveys which show favourable results have been published by those who are emotionally prejudiced in favour of this treatment (Allen, 1955); and that the majority of surgeons do not know how badly their operations turn out (Standley, 1955; Atkinson, 1956). Winnicott (1956) has said that even if he were convinced that a leucotomy could be good he would still believe it was bad; and he has observed that many of his patients have a deep fear of leucotomy. Hardenberg (1956) confirms this finding, adding that the fear may be so deep that it can be unearthed only with difficulty. Tow (1956) attributes much of this fear to scare articles in the lay press.

Published reports of results, for reasons of space, commonly confine themselves to overall assessments made by the authors and such objective observations as rates of discharge from hospital and proportions of patients at work. However, these are not always found convincing, and it can be and is argued that leucotomy represents some form of degradation. Better for the