THYROID TREATMENT OF ESSENTIAL HYPERTENSION—THE IMPORTANCE OF EARLY DIAGNOSIS*

PERICLES MENOF, M.B., B.CH. (RAND), M.R.C.P. (EDIN.), *Senior Physician, Johannesburg General Hospital*

In 2 series of cases of hypertension treated with desiccated thyroid[1,2] it was shown, firstly, that patients with renal hypertension failed to respond and, secondly, that the success achieved in the majority of patients was only partial, the blood pressure in these falling to levels intermediate between the original readings and the norm (group 2, Table I).

It is not difficult to account for these results. The explanation lies in the now accepted fact that hypertension of long standing, whatever its cause, produces narrowing of

TABLE I. RESPONSE OF HYPERTENSIVE PATIENTS TO THYROID TREATMENT

*Group**	*Blood pressure*	*No. of patients*	*% of total*
1	Fall to normal	46	14
2	Fall to intermediate levels	183	55
3	No fall	105	31
Total		334	100

* In the paper in which this table first appeared,[2] it was suggested that group 1 consisted of patients with 'pure' essential hypertension, group 2 of patients with mixed essential and renal hypertension, and group 3 of patients with predominantly renal hypertension.

the renal arteries and arterioles. The resulting ischaemia then sets in motion the mechanism of renal hypertension.[3-5] It follows that the majority of cases of hypertension which are labelled 'essential' are in reality of mixed aetiology, 2 distinct mechanisms being responsible for the elevation of the blood pressure. Of these only 1 responds to thyroid treatment.

If, then, we are to obtain more decisive results, it is obvious that we must begin treatment before renal hypertension supervenes. With this object in view a controlled experiment with patients whose pressures were only slightly raised was undertaken. In 12 consecutive experiments on 6 patients, the expected result was obtained.

Before giving the clinical details of these experiments, I propose to present the 2 cases which led me to conclude that such an experiment might prove helpful.

CASE 1

Mr. M.J.W., aged 26 years, married, a clerk.

History

Complaint: inclined to put on weight easily.
Symptoms: none.
Family history: mother obese.

Progress (Fig. 1)

Date	*Blood pressure (mm. Hg)*	*Pulse rate*	*Wt. (lb.)*	*Thyroid (gr.) (daily dose)*
1953				
3 June	140/90	76	174	None. Diet
3 July	140/90	76	173	1
10 July	140/90	80	173	2
24 July	140/90	80	172	2
21 August ..	128/80	80	170	3
4 September ..	124/80	70	167	3
25 September ..	126/72	68	164	3
23 October ..	136/70	64	160	3
28 November ..	130/70	72	157	3
1954				
8 January ..	124/70	72	156	None
5 February ..	124/76	60	157	None
29 March ..	132/94	62	161	3
30 April	132/80	78	164	3
28 May	128/74	68	163	3
25 June	136/82	82	163	3
23 July	128/80	72	166	4
26 August ..	128/74	74	166	4
1 October ..	126/64	66	166	4

Comment

Usually, the physician does not concern himself with blood pressures at this level. I did here, because I thought that a

* This paper — certain clinical details excepted — was read at the 6th International Congress of Internal Medicine held at Basle, Switzerland, 24-27 August 1960.

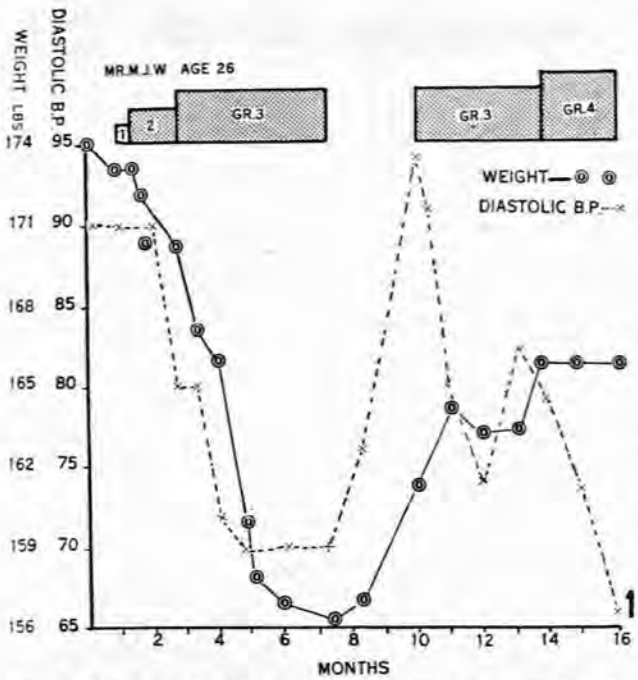


Fig. 1. Effects of thyroid on diastolic blood pressure and weight in early essential hypertension (case 1).

correlation between weight and blood pressure might prove of interest, particularly since some observers, such as Fishberg,[4] had stated that the fall in blood pressure in patients receiving thyroid is probably the result of weight loss. As will be seen from this record, the correlation is a very rough one. On 29 March 1954, with his blood pressure at 132/94 mm.Hg, the patient's weight was 161 lb. Six months later, while on thyroid, gr. 3 and later gr. 4 daily, he weighed 166 lb. His blood pressure, however, had fallen to 126/64 mm.Hg.

The most likely explanation of the relationship between obesity and hypertension is that both are manifestations of thyroid insufficiency.

The following details are worthy of note:

1. The remarkable consistency of the first 4 readings. Such readings, contrary to what was expected, were a feature of most of the cases diagnosed as early essential hypertension.
2. The disproportionate falls in the systolic and diastolic blood pressures. If we take 140/90 mm.Hg as the base line, then the maximum fall in the systolic pressure was from 140 to 124 mm.Hg, i.e. 16 mm.Hg, while the maximum fall in the diastolic pressure was from 90 to 64 mm.Hg, i.e. 24 mm.Hg.
3. The elevation of the blood pressure on stopping thyroid and its fall on resuming it.
4. The fall of the pulse rate on thyroid. This has been a common observation in hypertensive patients on this treatment. Note that towards the end of the experiment this patient was receiving a daily dose of 4 gr. of thyroid.

CASE 2

Mr. F.W.R., aged 47 years, married, a journalist.

History

Complaints—tiredness, discomfort in chest on walking, overweight.

Family history—not relevant.

Progress

Date	*Blood pressure (mm. Hg)*	*Pulse rate*	*Thyroid (gr.) (daily dose)*
February 1956	164/114	60	1
February 1957	148/104	58	2
March 1957	128/90	80	2
March 1958	144/94	68	2

Comment

This patient's weight, unfortunately, was not recorded. As will be noted, with 1 exception the readings were at yearly intervals. In March 1957 he stated that he was feeling particularly well. The chest discomfort left him shortly after he began taking thyroid.

These 2 cases, and more especially the first, suggested the possibility of treating essential hypertension at a very much earlier stage than is customary. They also suggested the feasibility of an adequately controlled therapeutic trial.

In the past such trials have not carried conviction because of our inability to neutralize the numerous variables normally influencing the blood pressure. I refer to such variables as the emotional state of the patient between readings and his emotional state at the time the reading is taken; the amount of physical exertion between and just before readings; the degree of narrowing of the renal arterioles and hence the extent to which the renal factor is responsible for raising the blood pressure; and finally, the rate at which the renal component of the hypertension is progressing.

Though such trials are unlikely to prove helpful in patients with established essential hypertension, they might provide reliable results in the early stages of the disorder. Firstly, because it would be unlikely that these cases would be complicated by renal hypertension and, secondly, because the responses to emotion, physical exertion and other factors would be so small as to be conveniently disregarded.

Such a trial was undertaken in a small series of patients who, I felt, could be diagnosed as having early essential hypertension. The results in 6 cases are given below. Two of the patients did not realize that it was their blood pressures in which I was primarily interested. I provided them with the thyroid and with the dummy tablets.

CASE 3

Mr. M.D.J., aged 32 years, married, a factory foreman.

History

Complaints—tiredness, frequent attacks of chest discomfort, overweight.

Family history—not relevant.

Progress

Date	*Blood pressure (mm. Hg)*	*Pulse rate*	*Wt. (lb.)*	*Treatment (daily)*
29 May 1953	140/96	88	204	Diet only
1 April 1957	142/94	90	206	Diet only
29 Oct. 1958	140/100	88	220	Thyroid, gr. 2
12 Nov. 1958	130/90	80	216	Placebo
26 Nov. 1958	140/100	80	213	Thyroid, gr. 2
10 Dec. 1958	134/86	80	213	Placebo
23 Dec. 1958	138/96	92	210	Thyroid, gr. 2
11 June 1959	132/88	72	210	Thyroid, gr. 2

Subjective Improvement

Definite. After 6 months on thyroid, gr. 2 daily, he stated that he no longer felt tired, that he was more energetic and that the chest discomfort had disappeared. Note the fall in pulse rate.

CASE 4

Mr. B.E.R., aged 35 years, married, a draughtsman.

History

Complaints—heavy feeling over left chest for past 2 weeks, giddy spell for 4 days.

Past history—1946, blood pressure queried by insurance company; 1953, blood pressure again queried by insurance company.

Family history—mother hypertensive (blood pressure 260/140 mm.Hg).

Progress

Date 1958	Blood pressure (mm. Hg)	Pulse rate	Wt. (lb.)	Treatment (daily)
29 Oct. ..	156/100	68	196	Thyroid, gr. 2
12 Nov. ..	146/92	68	196	Placebo
26 Nov. ..	150/100	76	196	Thyroid, gr. 2
10 Dec. ..	146/88	80	195	Placebo
23 Dec. ..	156/100	64	194	Thyroid, gr. 2
1959				
23 March ..	146/90	70	187	Thyroid, gr. 3
18 May ..	144/92	76	187	Thyroid, gr. 3

Subjective Improvement

Definite. No more giddy spells. Occasional chest discomfort, but of short duration.

CASE 5

Mr. A.G.M., aged 38 years, married, a draughtsman.

History

Complaints—drowsy, cannot concentrate, overweight.
Family history—mother grossly overweight, mental symptoms.

Progress (*Fig.* 2)

Date 1958	Blood pressure (mm. Hg)	Pulse rate	Wt. (lb.)	Treatment (daily)
28 July ..	154/96	96	215	Thyroid, gr. 1
11 Aug. ..	134/92	76	215	Thyroid, gr. 2
25 Aug. ..	136/96	76	207	Thyroid, gr. 3
9 Sept. ..	126/88	84	210	Thyroid, gr. 3
7 Oct. ..	130/90	74	205	None
21 Oct. ..	148/102	64	211	Thyroid, gr. 2
4 Nov. ..	130/86	68	209	Placebo
18 Nov. ..	140/98	72	209	Thyroid, gr. 2
2 Dec. ..	136/86	86	212	Placebo
15 Dec. ..	150/100	72	210	Thyroid, gr. 3
25 Dec. ..	136/90	78	208	Thyroid, gr. 3
1959				
24 April ..	134/94	70	214	Thyroid, gr. 2

Subjective Improvement
Uncertain.

CASE 6

Mr. I.H.M., aged 34 years, married, an accountant.

History

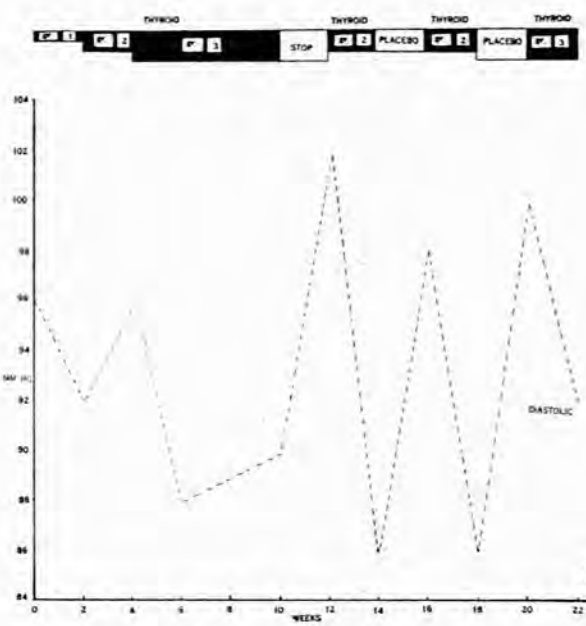
Complaints—tiredness, tendency to put on weight easily.
Family history—father and mother both have high blood pressure.

Progress (*Fig.* 3)

Date 1959	Blood pressure (mm. Hg)	Pulse rate	Wt. (lb.)	Treatment (daily)
21 Jan. ..	140/94	70	200	Thyroid, gr. 2
5 Feb. ..	128/84	72	200	Placebo
19 Feb. ..	146/100	66	200	Thyroid, gr. 3
5 March ..	134/86	74	201	Placebo
19 March ..	144/100	72	199	Thyroid, gr. 3
16 May ..	132/80	88	196	Thyroid, gr. 2

Subjective Improvement

Definite. Less tired. At last visit stated he was feeling tired again. This was considered to be from overdosage in view of the pulse rate, and the dose was changed to gr. 2 daily.



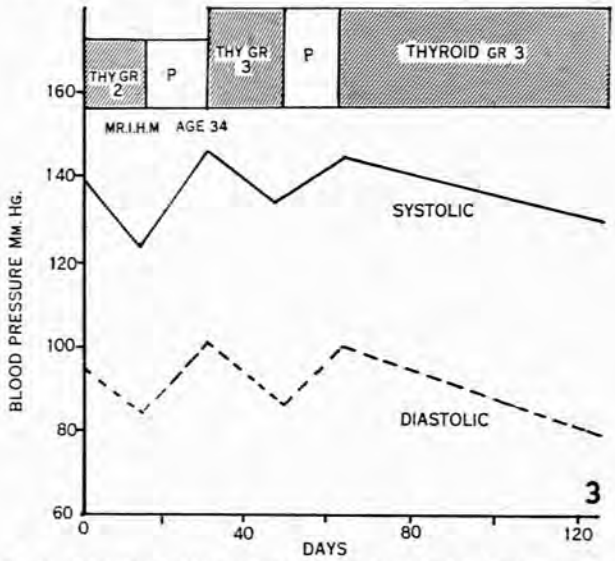


Fig. 2. Effect of thyroid and of placebo on the diastolic blood pressure in early essential hypertension (case 5).
Fig. 3. Effect of thyroid and of placebo on the blood pressure in early essential hypertension (case 6).

CASE 7

Mr. C.E.S., aged 25 years, single, a draughtsman.

History

Complaints—tendency to put on weight easily.
Family history—grandmother had hypertension.

Progress

Date 1959	Blood pressure (mm. Hg)	Pulse rate	Wt. (lb.)	Treatment (daily)
18 May ..	146/100	72	180	Thyroid, gr. 3
2 June ..	146/88	84	—	Placebo
16 June ..	146/104	82	—	Thyroid, gr. 3
30 June ..	144/82	76	—	Placebo
14 July ..	142/104	72	—	Thyroid, gr. 3
10 Sept. ..	130/90	76	172	Thyroid, gr. 3

CASE 8

Mr. D.N.C., aged 44 years, married, a manufacturer.

History

Complaints—tendency to put on weight easily.

Family history—both father and mother are hypertensive and obese.

Progress

Date	*Blood pressure (mm. Hg)*	*Pulse rate*	*Wt. (lb.)*	*Treatment (daily)*
1959				
18 Dec. ..	138/102	84	167	Thyroid, gr. 2
1960				
4 Jan. ..	120/90	82	—	Placebo
19 Jan. ..	140/108	96	—	Thyroid, gr. 2
2 Feb. ..	126/88	84	—	Placebo
15 Feb. ..	130/90	76	172	Thyroid, gr. 2

Note: The preparation of thyroid used in these experiments was that of the US Pharmacopeia, which requires an iodine content of approximately 0·2%.

COMMENT

Although the number of cases is small and although objections to this trial may be raised on other grounds, nevertheless, I regard the results as significant. I do so, not only because they are in accord with my earlier experiences in the treatment of hypertension with thyroid, but also for these additional reasons:

1. A number of clinicians in the past have reported a fall in blood pressure on thyroid medication. They include Oliver,[7] Clifford Albutt,[8] and Molnar.[9]

2. Means [10] observed a fall in blood pressure when most of the patients with myxoedema who had high initial pressures were treated with thyroid.

3. Joll[11] noted that 'following control of the thyrotoxic state, the blood pressures may rise rather than fall. Hill found that 50% of his follow-up patients had a systolic pressure of 150 mm.Hg or more and 20% had a pressure of 170 mm.Hg or more'.

4. Fatayeva[12] drew attention to a marked deficiency in thyroid function in 65% of patients with established hypertension.

5. Strisower *et al.*,[13] in their study of the physiological effects of *l*-triiodothyronine, recorded a fall in the blood pressure in all the 18 patients investigated.

6. Barnes[14] noted signs and symptoms of hypothyroidism in patients with hypertension and found that 'thyroid therapy is highly efficacious if the disease is not too far advanced'.

7. Finally, I consider the results significant because recent animal experiments support the hypothesis, first advanced in 1953, that thyroid insufficiency in relation to noradrenaline excess is the basic factor in the causation of essential hypertension.[15-17] A brief account of these experiments follows.

THYROID INSUFFICIENCY AND NORADRENALINE

In 1945 Marine and Baumann[18] showed that thiouracil depression of the thyroid of rats was followed by hyperplasia of, and increased secretion from, the adrenal medulla. At that time it was not known that there were 2 kinds of cells in the medulla, and it was assumed that the increased secretion was adrenaline. Recently, Hopsu[19] repeated the experiment in the mouse and showed that depression of the thyroid is followed by hyperplasia of the noradrenaline-secreting cells only (Fig. 4). Thyroidectomy produced the same results. Conversely, thyroid feeding caused a diminution in the volume of the noradrenaline-producing cells and diminished secretion from them (Fig. 5). Presumably this would also apply to the noradrenaline-secreting postganglionic nerve cells of the autonomic nervous system, since these are developmentally identical. Earlier, Eränkö[20] had shown that thyroid feeding caused a selective depletion of noradrenaline from the medulla in much the same way, though not as rapidly, as insulin causes a selective depletion of adrenaline.

That a similar adrenomedullary-thyroid relationship exists in man is suggested by the reactive enlargement of the thyroid gland which may occur during noradrenaline infusions, and at the height of the paroxysm of hypertension in phaeochromocytoma.[16]

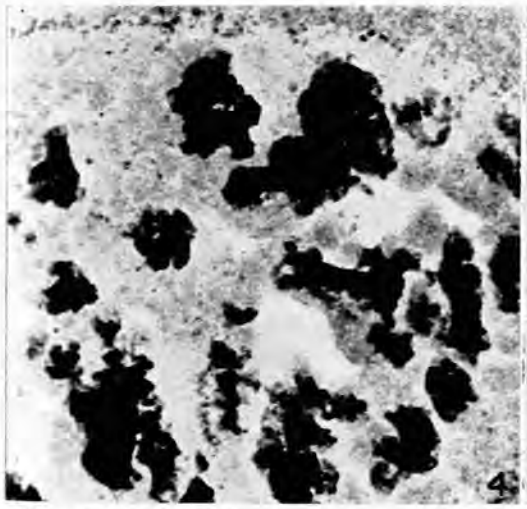


Fig. 4. Adrenal medulla of a mouse treated with thiouracil for 4-5 months — iodate reaction. Amount of iodate-positive tissue (= noradrenaline-secreting) increased and intensity of iodate reaction increased (after Hopsu).

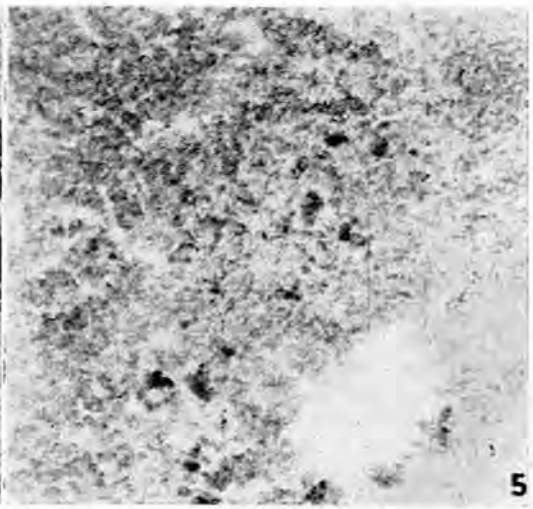


Fig. 5. Adrenal medulla of mouse treated with thyroid powder for 3 months. Iodate-positive tissue (= noradrenaline-secreting) very scanty. The whole medulla is colourless (after Hopsu).

DIAGNOSIS OF THYROID INSUFFICIENCY

It should be obvious from the facts just considered that thyroid insufficiency in the early stages of essential hypertension must be relative rather than absolute. Thyroid-function tests, therefore, are unlikely to prove helpful in diagnosis. How, then, are we to recognize the condition in its earliest phases? I suggest that the following indications might assist us:

1. A family history of hypertension or of any of its cerebral, cardiac or renal complications; a family history of obesity.

2. A tendency in the young or middle-aged to put on weight easily.

3. Complaints of undue fatiguability and substernal discomfort. (The classical symptoms of essential hypertension, namely, headache, giddiness, insomnia and palpitation are unlikely to be present, but their appearance, alone or in combination, particularly if precipitated by emotional stress, should be regarded with suspicion.)

4. The following objective findings: obesity, a diastolic pressure of 90 mm.Hg or over, and possibly an elevated serum-cholesterol level (above 200 mg. per 100 ml.).

With the help of these indications it should be possible to diagnose most of the cases sufficiently early to prevent the more serious consequences of this disorder.

THE RÔLE OF NORADRENALINE IN THE CAUSATION OF ESSENTIAL HYPERTENSION

That fears and anxieties may precipitate essential hypertension and may also suddenly raise the blood pressure to high levels in established cases, has been frequently reported by practising physicians and has been confirmed in recent years by the contributions of the psychosomatic school. Such rapid elevation of the blood pressure can occur only through the intermediation of the sympathetic nervous system. Since one of the transmitters of this system is noradrenaline, there can be little doubt that the elevation of the blood pressure here is from noradrenaline excess or an excessive reaction to noradrenaline.

This conclusion narrows the aetiological gap between phaeochromocytomic and essential hypertension. Clinically, the 2 conditions are indistinguishable — a point remarked upon by a number of observers.[21,22] In a recent case of mine, where death followed the removal of a phaeochromocytoma from the left adrenal, the postmortem findings were identical with those of long-standing essential hypertension. During the 15 years before his death this patient had been diagnosed repeatedly as having essential hypertension and had survived a cerebrovascular accident (hemiplegia with residual hemiparesis) and a myocardial infarction. If, then, the conditions cannot be distinguished in life and are inseparable in death, it follows that they are caused by fundamentally similar, if not identical, mechanisms.

It must be admitted, however, that they do differ in one respect, and that is in the amount of noradrenaline found in the urine. In most cases of phaeochromocytoma this is grossly in excess of normal, while in essential hypertension a slight elevation or none at all is the rule. In recent years even this distinction has ceased to be valid, because proved cases of noradrenaline-secreting phaeochromocytomas have been described, where at no stage in the development of the disorder has it been possible to demonstrate an increased excretion of this catechol amine.[23,24]

This suggests that the difference between the majority of the cases in these 2 disorders is not of great significance. It might well admit of some simple explanation, such as an abnormality in the rate or the method of inactivation of noradrenaline.

In this connection it is of interest to recall that Goldzieher[25] described the presence of phaeochromocytomas in chronic hypertension in his book *The Endocrine Glands:* 'The adrenals in hypertension are usually enlarged and heavier, but definite hyperplasia of the medulla is seen even in glands of average or less than average size. Histological evidence of hyperplasia repeatedly offered by the writer has recently been confirmed by Frei, Lacadou and others. The proliferation of both the medulla and extra-adrenal phaeochrome tissue is either diffuse, or produces small discrete nodules only of microscopic size. These nodules differ only in size from those found in paroxysmal hypertension . . .'.

This pathological evidence would suggest that phaeochromocytomic hypertension is merely an exaggerated form of essential hypertension.

SUMMARY

1. Further evidence is led in support of the hypothesis that thyroid insufficiency in relation to noradrenaline excess is the basic factor in the causation of essential hypertension.

2. The reason for the difficulty experienced in obtaining decisive results in the treatment of hypertension with thyroid is indicated.

3. The above clinical trial indicates that this difficulty may be overcome if essential hypertension is recognized early and treated before renal hypertension supervenes.

OPSOMMING

1. Verdere bewyse word aangevoer ter stawing van die hipotese dat tiroïed-tekort, in aansluiting aan 'n oormaat van noradrenalien, die grondliggende oorsaaklike faktor is by essensiële hipertensie.

2. Die rede vir die moeilikheid wat ondervind word om beslissende resultate te verkry by die behandeling van hipertensie met tiroïed, word aangedui.

3. Die voorgaande kliniese ondersoek dui aan dat die moeilikheid oorkom kan word as essensiële hipertensie vroeg raakgesien word en as behandeling toegepas kan word voordat renale hipertensie intree.

I should like to thank the Warner-Lambert Pharmaceutical Company, Morris Plains, New Jersey, USA, for the supply of dummy tablets of their thyroid preparation, and the Photographic Unit of the Department of Medicine of the University of the Witwatersrand for their assistance with the illustrations.

REFERENCES

1. Menof, P. (1950): S. Afr. Med. J., **24**, 172.
2. *Idem* (1952): *Ibid.*, **26**, 967.
3. Floyer, M. A. (1951): Clin. Sci., **10**, 627.
4. Wilson, C. (1953): Lancet, **2**, 632.
5. Moyer, J. H., Heider, C., Percy, K. and Ford, R. V. (1958): Amer. J. Med., **24**, 164 and 177.
6. Fishberg, A. M. (1954): *Hypertension and Nephritis*, 5th ed. London: Ballière, Tindall and Cox.

7. Oliver, G. (1916): *Studies in Blood Pressure*. London: Lewis.
8. Allbutt, C. (1925): *Arteriosclerosis*. London: Macmillan.
9. Molnar, B. (1929): Ther. d. Gegenw., **70**, 191.
10. Means, J. H. (1948): *The Thyroid and its Diseases*, 2nd ed. London: Lippincott.
11. Joll, C. A. *In* Rundle, F. F. ed. (1951): *Diseases of the Thyroid*, 2nd ed. London: Heinemann.
12. Fatayeva, M. N. (1956): *International Conference on the Peaceful Uses of Atomic Energy*, vol. 10, p. 215. New York: United Nations.
13. Strisower, F. H., Gofman, J. W., Strisower, B. and de Lalla, O. (1958): J. Clin. Endocr., **18**, 721.
14. Barnes, B. (1959): Fed. Proc., **18**, 8.
15. Menof, P. (1953): S. Afr. Med. J., **27**, 418.
16. *Idem* (1954): Lancet, **2**, 996.
17. *Idem* (1956): S. Afr. Med. J., **30**, 986.
18. Marine, D. and Baumann, E. J. (1945): Amer. J. Physiol., **144**, 69.
19. Hopsu, V. K. (1960): Acta endocr. (Kbh.), suppl. 48.
20. Eränkö, O. (1952): Acta anat. (Basel), suppl. 17, part I.
21. Green, D. M. (1946): J. Amer. Med. Assoc., **131**, 1260.
22. Goldenberg, M. (1951): Amer. J. Med., **10**, 627.
23. Litchfield, J. W. and Peart, W. S. (1956): Lancet, **2**, 1283.
24. Reutter, F. W., Zikeli, M. F., Hamlin III, J. T., Thorn, G. W. and Friend, D. G. (1957): New Engl. J. Med., **257**, 323.
25. Goldzieher, M. A. (1939): *The Endocrine Glands*. New York and London: Appleton, Century.