Essential hypertension and its treatment by the family physician

A study of sixty-one cases

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SUMMARY—It has been demonstrated (*e.g.* Leishman 1959) that the lowering of raised blood pressure before it has produced symptoms is of long term benefit to the patient.

Sixty-one patients, 28 men and 33 women, with essential hypertension have been studied over an eight-year period. The efficiency and validity of developing a standard method of treatment which is only varied when response is inadequate or negative is evaluated. The significance of hypertension without evident cause is discussed. The effect and safety of long-term treatment with a combined preparation of reserpine and bendrofluazide is demonstrated. The period of study covers just over 84 patient-years.

The average reductions in blood pressures over 18 months were from 223/121 to 154/85 in men, and from 231.5/121.5 to 154/87 in women, the overall figures for both sexes being from 227/121 to 154/86 mm Hg.

THIS study was undertaken to assess the efficiency and safety and long-term results of choosing in general practice one standard treatment to lower raised blood pressures in patients with hypertension without evident cause who have no other significant disease.

The criteria governing the choice of drugs were (1) it had adequately to reduce raised blood pressure, (2) it had to be easy to administer, *e.g.* one tablet is always preferable to two provided the effect is the same, (3) it had to have minimal or no side-effects, (4) if possible the administration of supplements such as potassium was to be avoided, (5) it had to be safe to administer with minimal laboratory control.

Reserpine and bendrofluazide fitted these requirements and a preparation, Abicol (Boots) containing reserpine 0.15 mg and bendrofluazide 2.5 mg in one tablet was chosen, with the added object of assessing whether common criticism that it is undesirable not to be able to vary separately the dose of each constituent (Proplist 1969) in a combined preparation, had any basis in practice.

Pharmacology

1. *Reserpine.* The plant *Rauwolfia serpentina* grows in India, Ceylon and the Malay Peninsula, to a height of about three feet and bears white or pinkish flowers. It is a genus of the Apocynaceae family, and was named after Leonard Rauwolf, a sixteenth century German physician and botanist who travelled extensively in the East, seeking medicinal plants.

The active principles are contained in its roots and preparations of these have been used since ancient times as remedies for fever, snake bite, dysentery, insomnia, hypochondria, insanity and anxiety. It has been known in Europe for 300 years.

Fourteen alkaloids have been isolated from the root. Reserpine was reported and named in 1953 by Bein. It is the only markedly-active alkaloid, having a hypotensive and sedative action on the central nervous system. For instance it has been shown (Plummer

et al 1954) that an aggressive monkey can easily be handled after an I V injection of 1 mg/Kgm.

Reduction of blood pressure by Rauwolfia in essential hypertension was reported in 1933 by Chopra, Gupta and Muckerjee, and in 1942 by Bhatia. A controlled trial was carried out by Vakil in 1949.

The main advantages of reserpine over other and more potent drugs are:

(a) Its smoothness of action due to its cumulative properties—taking one to two weeks to exert an initial effect and up to eight weeks or even longer to exert its maximum effect. This makes it particularly useful in the older age group.

(b) No tolerance or addiction (Wilkins 1954); indeed once control of hypertension is achieved, the dose can nearly always be reduced.

(c) Maintenance on very small dosage.

(d) The absence of postural hypotension in patients receiving it (Freis and Ari 1954). This makes it particularly useful for stabilization of patients in general practice.

(e) A synergistic effect with other hypotensive drugs including diuretics and sympathetic blocking drugs.

Reserpine was originally thought to exert its effect centrally (Plummer *et al* 1954), but was soon shown (McQueen *et al* 1955) to act peripherally by depleting the vessel walls and the adrenal medulla of noradrenaline, the principal sympathetic transmitter. It may also deplete the brain of amines thereby being responsible for mental depression; this effect is extremely rare if the daily dose is kept below 0.5 mg.

2. *Bendrofluazide.* The use of thiazides as diuretics was first reported in 1957 (Tapia *et al*) and this was quickly followed in the same year by reports (Freis and Ari 1954) that chlorthiazide had a hypotensive effect on its own and this effect was enhanced if it were combined with ganglion blocking drugs or reserpine.

Bendrofluazide, a member of the benzothiadiazine group of compounds, is a diuretic over 100 times more potent than chlorthiazide, promoting the excretion of water with sodium and chloride ions in approximately equimolar amounts. It is safe (Kobinger and Katic 1960) and when used to treat hypertension and congestive cardiac failure in fairly high dosage, causes comparatively unimportant electrolyte disturbance, and less potassium depletion than chlorothiazide (Berthelsen and Eilersen 1960). Because of this, bendrofluazide may be administered in moderate dosage for extended periods without resort to potassium supplement, although serum electrolyte levels should be checked at reasonable intervals. Grieble and Johnston in 1962 found that when bendrofluazide was added to reserpine in the treatment of 43 patients, there was a further reduction in blood pressure. They also treated 68 patients with bendrofluazide alone on a long-term basis, and found that potassium depletion was not a problem, concluding that addition of the latter was unnecessary in the long term treatment of hypertension. The fact that the combination of reserpine and bendrofluazide enables a reduction in the dosages of each of these drugs whilst producing an adequate therapeutic response, renders the likelihood of depression or of potassium depletion (the most serious side effects), even less likely.

Method

All patients had a full personal and family history taken, a complete physical examination including ophthalmoscopy, haemoglobin estimation and urinalysis. Blood urea estimation and an IVP were carried out if considered necessary, and all patients with complicating diseases relevant to the production of hypertension were excluded.

After assessment, each patient had his or her condition, and the significance of hypertension explained to them, and was prescribed two to four tablets of Abicol daily in divided doses to lessen any possible gastro-intestinal side effects. The intervals at which patients were seen over the long term were dictated by their response to treatment.

Where response was inadequate or negative, pargyline, guanethidine or bethanidine was added.

No case had malignant hypertension, nor did any patient have existing renal disease, although two men had a past history of this, one having had a nephrectomy for nephrolithiasis 20 years previously. No patient had haemoglobin outside the normal range, and in every case the urine was free of protein and sugar.

The recording of blood pressure

The techniques of blood pressure estimation have been very well discussed recently by Holland (1968). In the present study the right arm was used for recording the pressure. After 100 serial estimations, both sitting and standing, it was found that in patients receiving Abicol, there was no recordable difference in pressure in these two positions. However, two other factors influence the readings considerably. The first is the position of the arm, which must be hyperextended. An angle of 45° or over at the elbow can raise the reading by up to 20 mm mercury. The second factor is the speed at which the arm band is allowed to deflate. If the air is allowed to escape too rapidly when using a mercury sphygmomanometer, the rate of the fall in pressure in the arm band exceeds the rate of fall of the mercury, and an unduly high reading is obtained. This effect will vary with the efficiency of the machine used. As regards the actual readings recorded in this article, the systolic did not present a problem. However, as is well known, the diastolic may present itself in two ways, the sounds either suddenly diminishing and almost as rapidly disappearing or suddenly diminishing, but taking an extra few mm Hg to disappear. Diastolic pressures of this latter type have been averaged and the mean pressure of the two readings has been recorded.

Weight reduction

Wherever necessary and possible, weight reduction was energetically pursued, and some of the most dramatic results (cases M3 and M18) were obtained when considerable weight reduction was achieved.

Dosage

This has varied from an initial dose of three tablets daily (reserpine 0.45 mg + bendrofluazide 7.50 mg) rising in one case to four tablets daily (reserpine 0.60 mg + bendrofluazide 10.0 mg) for a short time, to a maintenance dose of half a tablet daily (reserpine 0.075 mg + bendrofluazide 1.25 mg).

Patient presentation

Four patients, two men and two women, were discovered to be hypertensive on routine examination. The others, 24 men and 31 women, presented with some symptom or pathological condition. In several cases, the complaint was a vague malaise, the patient admitting to headaches, giddiness, dyspnoea of effort or anxiety only on further questioning (table I).

The commonest presentation was dyspnoea of effort, and it is likely that this symptom had been present for some time, but had been so insidious in its progression that it had been largely ignored or put down to increasing weight or just age. The second commonest presentation was by a cerebrovascular accident. Fortunately, these patients all had minor lesions save one whose residual hemiparesis has prevented her working since.

The frequency of this mode of presentation as actual disease rather than symptom, is in accord with the figures of 26 life insurance companies from 1935–54 compiled by the Metropolitan Life Insurance Company. These figures show that the rise in mortality with increasing arterial pressure is steepest (6.2 times the expected rate) for lesions of the central nervous system. This is probably because these patients have little, if any, previous warning of impending disaster. Their cardiac and arterial muscle seems to have

coped with the rise in tension remarkably well, but in the end some CNS capillaries collapse. For instance a pressure such as 260+/160 was recorded in a patient with a stroke who had not reported any cardiac symptoms previously. His case history and one other illustrate this point:

TABLE I

Presentation	*Number presenting*		*Total*	*Code*
	Men	*Women*		
Dyspnoea of effort	7	7	14	D
Cerebrovascular accident	6	7	13	CVA
Headaches	2	4	6	H
Giddiness	2	5	7	G
Cardiac failure	2	3	5	CF
Routine examination	2	2	4	R
Angina of effort	1	1	2	A
Myocardial infarction	1	0	1	MI
Life insurance examination	1	0	1	RL
Anxiety state	1	1	2	N
Pregnancy, essential hypertension	0	2	2	PH
Pregnancy, toxaemia	0	1	1	PT
Carotid thrombosis	1	0	1	Car T
Retinal thrombosis	1	0	1	Ret T
Paroxysmal nocturnal dyspnoea	1	0	1	PND
Total	28	33	61	

Case 1. In December 1963 a man, aged 51 years, had a severe epistaxis. He was plethoric with a blood pressure of 210/120, grade II hypertensive retinopathy and weighed 198lbs, height 5ft. 8in. He had had a few week's blurring of vision in his right eye in January 1953. Blood pressure then not known. After six weeks of weight reduction and reserpine 0.25 mg tds his blood pressure was 170/80 and weight 175lbs. Twelve weeks later weight 168lbs., blood pressure 180/80. In January 1966 blood pressure was 200/110 and weight 177lbs. No further treatment is recorded. Eighteen months later in June 1967 he had a sudden mild right hemiplegia. The blood pressure was 260+/160. He was rested, again prescribed a strict salt-free diet and Abicol, one tablet tds. Three weeks later his blood pressure was 210/120-110. Pargyline 25 mg tds was added. Two weeks after this he only had residual weakness and speech slurring, and his blood pressure was 140/90. He weighed 175lbs, blood urea 54 mg per cent., serum potassium 3.9m. equiv/litre, IVP normal. With resumption of duties as a market gardener, blood pressure has risen slightly until it is now 160/100, weight being 161lbs. Treatment—Abicol tablets one bd, pargyline 25 mg tds.

Case 2. In November 1965 a secretary, aged 45 years, had an unheralded severe left-sided hemiplegia. She made a slow but remarkably good recovery but, although now able to live a fairly normal domestic life, has not been capable of gainful employment again. In 1942, aged 21 years, she was overweight and was slimmed on and off for many years. In 1955, aged 35 years, superannuation examination revealed a blood pressure of 230/130. An IVP was normal, and no treatment was prescribed. In 1963 her blood pressure was 228/130 and weight 173lbs. Abicol was prescribed, one tablet tds, plus diet. A month later her blood pressure was 185/110 and her weight was 147lbs. She then defaulted, and 19 months after this had her cerebral haemorrhage. Her blood pressure is now well controlled around 135/90. This case illustrates how long hypertension may be present before catastrophy, and that blood pressure screening is probably as important as any other screening test such as urinalysis. The critical importance of patient education and follow up is also revealed.

Results

All patients save one are still alive and the results for 56 patients extend over at least 18 months. One man defaulted and another cannot be traced and his present condition is unknown. Toxicity was not encountered and no serious side effects were seen. Postural hypotension was not produced, and neither tolerance nor addiction

occurred. Only one patient with generalized atheroma producing multiple strokes died.

Treatment with Abicol had to be abandoned because of side effects in one man and four women, 8.2 per cent of the total, and one man who has had mild nasal congestion has continued with Abicol. In four cases, all men (6.5 per cent of the total), control with Abicol alone had to be abandoned because of inadequate control. There were no escapes from control among the women patients.

Reduction in blood pressure

That reserpine and bendrofluazide in combination are effective hypotensive therapy is demonstrated by the average falls in blood pressures. In men the average initial pressures were 223/121 falling to 166/90 after six months of treatment, and 154/85 after 18 months. In women the picture was similar with average initial pressures of 231.5/121.5 falling to 165/90 at six months and 154/87 at 18 months. The overall figures for both sexes being 227/121 initially, 165.5/90 at six months and 154/86 at 18 months (table II).

TABLE II

AVERAGES OF BLOOD PRESSURES IN MEN AT INTERVALS IN WEEKS DURING TREATMENT

Week	*0*	*2*	*4*	*24*	*78*	
Blood pressure	223/121	182/98	168/91	166/90	154/85	mm Hg.

AVERAGES OF BLOOD PRESSURES IN WOMEN AT INTERVALS IN WEEKS DURING TREATMENT

Week	*0*	*2*	*4*	*24*	*78*	
Blood pressure	231/121	174/94	168/88	165/90	154/87	mm Hg.

Chronic or intermittent control

The ideal hypotensive agent would reduce the arterial pressures and leave them permanently reduced when it was withdrawn. As, however, we are, in essential hypertension, fighting a constitutional or inborn diathesis (Pickering 1965 and Platt 1964) which may have been triggered and/or exacerbated by environment, this diathesis will reassert itself if we cease countermeasures. Because of this, it was found impossible in any cases to withdraw treatment save for limited periods. The majority needed chronic treatment, *i.e.* 22 or 81.5 per cent of men (five or 18.5 per cent managing on intermittent therapy) making overall figures of 76 per cent on chronic and 24 per cent on intermittent therapy for both sexes.

Side effects

1. *Depression*—In men there were no cases of depression resulting from treatment. In women there were two cases (3.3 per cent). In one treatment was abandoned after four weeks in a 77-year-old woman who had presented with an anxiety state, and a blood pressure of 240/140. The reduction in blood pressure was dramatic, but it was thought on reassessment that she was a depressive anyhow. The second woman had been treated for over two years when she complained of feeling depressed, and was transferred to guanethidine for maintenance.
2. *Gastro-intestinal disturbance*—This was a more troublesome side effect and has

been noted to be so in other patients not included in this series. The treatment had to be abandoned completely because of this in one man because of the re-appearance of a gastric ulcer, and two women because of colic and diarrhoea, a total of three (4.9 per cent of the total).

3. *Nasal congestion*—This can be an annoying side effect, presumably due to the inhibition of sympathetic end-effect in the nasal mucous membrane, but is rarely severe on this dosage of reserpine. It only occurred in one man in whom it was not severe enough to stop treatment. An overall incidence of 1.65 per cent.
4. *Gout*—No case of gout occurred.

Lack of, or poor control

In no case did poor control necessitate complete cessation of treatment with Abicol. However, the exhibition of Abicol alone had to be abandoned in four men (in no women was this necessary). In one case the initial control was good, but six weeks later on resuming activity, the pressure rose to 230/135. Over the next 18 months, methyl dopa was prescribed, but abandoned due to the occurrence of impotence; likewise bethanidine because of side effects. He is now well controlled on Abicol four tablets plus guanethidine 100 mg daily. Two others also quickly escaped control, but were subsequently stabilized by adding pargyline 25–257 mg daily with the usual precautions which incidentally help to reduce weight. The other man is now controlled on two Abicol tablets plus 50 mg of bethanidine daily.

Discussion

Some authors (*e.g.* Bath *et al* 1967) have stated that the majority of hypertensive patients in this country are being treated with guanethidine or methyl dopa with or without an oral diuretic. This may be so in hospital clinics, but in general practice, diuretics or reserpine or both are almost certainly the initial choice and reserpine is probably the most widely used drug in this condition. Many authorities however, have dismissed reserpine as being unsafe (*e.g.* Whitfield 1966) and ineffective, in severe hypertension, and difficult to adjust in dosage when combined with a diuretic in the same preparation (Leishman 1968, Proplist 1969). This paper is an attempt to demonstrate that these views are not necessarily true. In this study, all patients expressed a preference for one tablet rather than two, and, as the treatment was shown to reduce blood pressure adequately and safely, it is maintained that a single preparation containing reserpine and bendrofluazide is a safe, effective and convenient form of therapy. It was also found that with scored tablets, the dose was variable within small limits. The practical advantages and results of using a combined preparation outweigh the disadvantages save in special circumstances.

The normal average blood pressures in man have long been accepted as being 120 mm Hg systolic and 80 mm Hg diastolic, and it is often difficult for the physician to decide at what point, in any departure from these figures, treatment is justified. However, there is clear evidence that any significant rise above the normal is harmful, and that reducing this rise is of benefit to the patient in decreasing morbidity and increasing expectation of life (Actuarial Association of America 1941, Leishman 1959).

Leishman (1968) in a full review of the treatment of hypertension, quotes his figures of 1959 indicating that one third of men with hypertension, with diastolic pressures below 120 mm Hg die before the age of sixty. He says " the tendency today is to treat hypertension of lesser grade than formerly and it seems reasonable to assume that in men, unless perhaps over the age of 65, even a diastolic pressure of 100 mm Hg may with advantage be lowered ". He goes on to recommend a combination of rauwolfia and a diuretic as the first line of attack, but says there is less merit in carrying this out with combined preparations. He then goes on to say that " while this combination may be

expected to be successful when the diastolic pressure does not greatly exceed 110 mm Hg, above this level it is usually necessary to resort to an adrenergic drug." Some authorities, however, go so far as to say that rauwolfia should never be used because of the risk of depression (*e.g.* Whitfield, 1966).

Thirty, or even 20, years ago, this problem was largely academic, but now with potent drugs at our disposal if blood pressure can be reduced with no harmful or distressing effect upon the patient, the physician has a duty to prescribe a hypotensive drug, but at what point can still only be answered by exercising the art as opposed to the science of medicine, and as yet no laboratory test or computer can provide this answer. Indeed, the issue has been confused by the attempts of many authors to define qualitatively high blood pressure. This is rather like attempting to define the exact point at which a tall man becomes a giant, or a short one a dwarf. It is impossible without providing some arbitrary figure which is in effect an artefact. However, some attempts are shown in table III.

TABLE III

DIVIDING LINES BETWEEN 'NORMOTENSION' AND 'HYPERTENSION'

120/80	S. C. Robinson and M. Brucer 1939
130/70	F. J. Browne until 1947
140/80	D. Ayman 1934
140/90	G. A. Perera 1948
150/90	C. B. Thomas 1952
160/100	P. Bechgaard 1946
180/100	A. M. Burgess 1948
180/110	W. Evans 1956

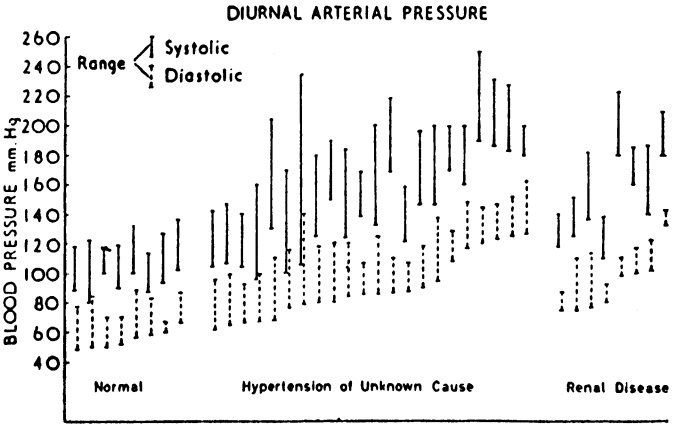

Figure 1

The problem is made even more difficult by the known diurnal variations in blood pressures in both normal and hypertensive subjects (Richardson *et al* 1964). This has also been discussed by Pickering (1965), and is illustrated by figure 1 which he quotes.

If we have avoided the danger of falling into the trap of attempting to define the point at which hypertension begins we must be even more wary when attempting to define the point at which treatment must be initiated. Hypertension without evident cause is best approached quantitatively (Pickering 1964) and the possible disastrous results of adhering to a rigid qualitative definition of either the condition or the point of interference are well illustrated by the following case:

Case 3. In January 1966 a dyspnoeic 50-year-old man with ankle oedema walked into the consulting room. On examination, râles both lung bases, triple rhythm 150/min, blood pressure 260/140. *Investigations:* Hb. 15.0 mg per cent, blood urea 29 mg per cent urine—protein and sugar free. Subsequent I V P—normal.

Previous history: Noted to be hypertensive on discharge from army 1946—no figure available—no instructions given for surveillance. *May* 1961—blood pressure 230/130 (superannuation examination), referred to general practitioner who referred him to consultant who reported " On the whole, I am inclined to follow Professor McMichael's teaching and take no action provided the diastolic is around 120/130 . . . it looks as if he has had a '*mild*' (author's italics) hypertension for 15 years, and if one attempted to treat it or investigate it further, it might send him into an anxiety state with no good effect."

December 1964—Blood pressure 260/160, fundi grade II. A further outpatient appointment made

which he failed to keep. The effort to play the condition down was later admitted by the patient to be a factor in this. Business took him away at the time. *January* 1966—congestive cardiac failure.

Pickering (1965) has also discussed the significance of the casual recordings of blood pressures and demonstrated that these may be misleading. However, we have to make a decision at some point, and as not all patients can have continuous sleeping intra-arterial pressures recorded, our decisions must perforce be based on casual readings, albeit under the best possible conditions. This may not be as unscientific as it seems because in the hypertensive subject, elevation of the blood pressure not produced in the normal subject as a response to minor stresses, such as consultation with his physician, most probably acts in a two steps upward, one step downward fashion, the summation of these responses eventually producing persistent hypertension and pathological change. Therefore, patients with higher than normal casual blood pressure readings should be advised to visit their physicians regularly once or even twice a year. The risk of producing a neurosis by this advice is slight as most patients now take an intelligent 'scientific' interest in their health, and even neurosis is far preferable to an unheralded stroke at a premature age.

The dilemma can be well demonstrated by the following case histories:

Case 4. A woman died in 1963, aged 81 years, of heart failure and Parkinsonism. She had had four normal pregnancies. She was hypertensive during her pregnancies, and in 1932 Sir John Parkinson wrote (the letter is still in her file) "This patient is hypertensive with a blood pressure of 210/120. Her expectation of life cannot, therefore, be good. She may, however, live a normal active life for very many years." How right he was! Nevertheless, she might have been spared the disability of her extreme tremor which troubled her for many years before her death if it had been possible to reduce her blood pressure at an early stage.

Case 5. In 1967 a woman, aged 40 years, had an attack of acute pulmonary oedema in her physician's consulting room, blood pressure 180/120. In hospital ECG and x-ray revealed complete left bundle branch block and left ventricular hypertrophy. Urine and renal function were normal. She had had two pregnancies. Two weeks before her first delivery, blood pressure was 140/105. In 1955 she had an intrauterine death of 24 weeks. Blood pressure was 160/100. No albuminuria. She was advised to have no more children, but not advised to have her blood pressure regularly checked. During the previous one or two years before her heart failure she had complained of malaise, fullness in the head and dyspnoea on exertion. She had asked to have her blood pressure taken, but had been told not to worry!

Conclusion

It is concluded from this study that reserpine in conjunction with bendrofluazide in the same tablet is an effective safe and convenient agent for the reduction and long term treatment of raised blood pressure when used as standard treatment in the ambulant patient in general practice.

Because of its lack of side effects, smoothness in stabilization, and synergistic action with other hypotensives, this preparation can be recommended as the initial treatment of choice for essential hypertension, more sophisticated synthetic drugs being added or substituted later if necessary.

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The College of General Practitioners. *Research Newsletter* No. 4. April 1954.

The Research Committee formulated their plan for general practitioner research along three lines; research by college members into subjects chosen by the research committee and in which any member of the college could participate; research by groups of members having common interests, and research by individual practitioners. When these plans were made the committee were quite unaware that ' collective ' investigation had been attempted before.

The idea of collecting information from a number of doctors was, so far as we can ascertain, first suggested by Heberden. Fothergill, in 1775, drew up a sketch of the influenza prevalent in that year in London and circulated it to many of his friends practising all over the country. These reports were collected and published in the third volume of the *Transactions of the College of Physicians.* From that date on, many attempts at collective investigation were made. In 1834 and again ten years later, information was requested in the Provincial Medical Journal on various subjects. In 1847 an enquiry into the treatment of burns was instituted and the replies were published fortnightly in the *British Medical Journal.* Thomas Hunt in 1948 instituted an inquiry into the medical action of arsenic. The responses to these various attempts were not altogether satisfactory and it was not until 1880 that plans were made to collect information on a grand scale. In that year the British Medical Association set up a committee of seven to institute inquiries into disease and treatment. This committee was a powerful and influential one and immediately set about its work with zeal and energy. Reports were published in 1882 in the Journal and in 1883 and 1884 as special volumes. Various subjects were chosen for investigation, care being taken that some imperfectly understood point should be investigated. Thus the infectivity of tuberculosis was the first subject to receive a report. This was followed by reports on the infectivity and the epidemic incidence of pneumonia, on chorea and heart disease, on acute rheumatism and on diphtheria. These reports must have been of considerable value at the time of their publication. The method used by the committee was first to choose a subject and then to publish in the Journal a short article on it, giving the reasons why certain points needed special attention by the investigators. Cards were then issued through the provincial committees set up by the Branches of the Association.