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RESULTS OF HYPOTENSIVE THERAPY IN ARTERIAL HYPERTENSION

BASED ON EXPERIENCE WITH 497 PATIENTS TREATED AND 156 CONTROLS, OBSERVED
FOR PERIODS OF ONE TO EIGHT YEARS

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The value of hypotensive drug treatment in malignant hypertension is now generally accepted, its effect having become obvious within a comparatively brief period by reason of the extremely poor prognosis in the untreated cases. The effects of treatment in less severe cases cannot be so readily assessed because of the slower rate of attrition amongst untreated cases. Sufficient time has now elapsed, however, to make it worth while to examine the progress of patients in the less severe categories as well as those with malignant hypertension. In the present report the results of treatment over a period of eight years (1950-7) are reviewed. The fate of a control untreated series initiated at the same time is also reviewed.

Material

Of 805 patients investigated at the Dunedin Hospital Hypertension Clinic between January 1, 1950, and December 31, 1957, 646 patients were considered to be suitable for hypotensive therapy. Of these, 497 patients accepted treatment and have been maintained on treatment for from one to eight years—that is, up to December 31, 1958, or to the time of death. Eighty-two patients declined therapy for various reasons, largely because of the inconvenience of frequent attendance at the clinic or because of the side-effects that they had been warned they must expect. Few grade 4 cases were available as controls, and seven well-documented patients with malignant hypertension who had been admitted to the Dunedin Hospital prior to January 1, 1950, were added to the list of controls, bringing the total number of patients who received no hypotensive therapy to 89.

Additionally, there were 67 patients who received a period of treatment but were unwilling to continue with it. These have been considered as a separate series of controls, the date of stopping treatment being regarded as the start of the control period. The mean duration of therapy in those abandoning treatment was 16.6 ± 14.3 months. A more detailed analysis showed that the shorter the period of treatment before becoming a control the higher was the mortality. Thus the mortality after ceasing treatment was 74% in those who had up to

six months' treatment and then stopped, 50% in those who stopped after 7-12 months, 57% after 13-18 months, 44% after 19-24 months, and 42% after 25 months or more.

In our analysis of results we have compared results in the treated with those in the complete control series (Charts 1, 3, and 5), but we have also made a comparison omitting the patients who received any form of therapy, thereby restricting the analysis to those who elected not to have treatment from the outset (Charts 2, 4, and 6).

The annual intake of new patients has varied over the years. The number of controls available diminished during the period of observation (Table I). Distribution by sex is shown in Table II. Among the 653 patients, females outnumber males in the ratio of nearly 2:1. The proportion of females is greater in the control than in the treated group. There were also slight differences in the two groups in respect of age (Tables III and IV).

TABLE I.—Annual Intake of Patients Treated and Controls

	Before 1950	1950	1951	1952	1953	1954	1955	1956	1957	Total
Controls	7*	31	26	11	22	15	24	8	12	156
Treated	0	36	59	73	78	65	74	59	53	497
Total	7	67	85	84	100	80	98	67	65	653

* Additional malignant hypertensive controls studied before January 1, 1950.

TABLE II.—Distribution of Males and Females Between Treated and Control Groups

	Control	Treated	Combined
Female	115 (73.7%)	303 (61%)	418 (64%)
Male	41 (26.3%)	194 (39%)	235 (36%)
Total	156* (100%)	497 (100%)	653 (100%)

* Includes 7 malignant hypertensive control patients studied before January 1, 1950.

TABLE III.—Age Grouping of Treated Patients and Controls

	-20	20-29	30-39	40-49	50-59	60-69	70+	Total
Treated	4	13	54	138	176	103	9	497
Control*	0	3	10	33	61	39	10	156
Total	4	16	64	171	237	142	19	653

* Includes additional 7 malignant hypertensive control patients studied before January 1, 1950.

TABLE IV.—Average Age of Patients at the Time of Beginning Treatment or Being Accepted as Controls

	Control		Treated	
	Alive	Dead	Alive	Dead
No. of patients	74	82	343	154
Average age on acceptance	55.1	54.1	50.7	50.9

The average age at the time of assessment was 54.5 years for the controls and 50.8 for the treated cases; allowance has been made for this in the methods of analysis used. Table V shows the constitution of the two series in terms of the severity of the retinal changes—grading of Keith, Wagener, and Barker (1939). It can be seen that, as judged by retinal grading, a higher proportion of mild cases occurred in the controls than in the treated group.

We are not aware of any tendency for more severe cases within the retinal grades to be allotted to the control series. In fact, the reverse was probably the case, patients with more severe manifestations being particularly urged to accept treatment.

The aim of therapy was to maintain the blood-pressure at as nearly normal levels as possible throughout the 24-hour day. The drugs used during the period 1950–7 included the ganglion-blocking agents hexamethonium (mainly parenterally), pentolinium, chlorisondamine, and mecamlamine (almost exclusively orally). During the latter half of the period these were supplemented in many cases by a rauwolfia alkaloid—reserpine, rescinnamine, or canescine. In a small number of cases one of these sufficed alone.

Percentage mortality of treated hypertensives and controls. Retinal grades 4, 3, and 2 in an eight-year follow-up.

Duration of Observation and Sex

As already mentioned, there was a relatively higher allocation of cases in the earlier years of the observation period to the control group, which consequently has a longer average period of exposure. Additionally, there was a difference in the constitution of the two series with regard to sex, there being a higher proportion of females among the control cases. This would tend to favour the latter because of the generally better prognosis for hypertension among females than among males. However, it is possible to take both these points into consideration by plotting the percentage survival at yearly intervals separately for the two sexes.

Retinal Grading

Table V indicates that, as judged by retinal grading, a higher proportion of mild cases occurred among the controls. This is allowed for by displaying the results for each grade separately in the Charts. The points in these graphs have been determined by the statistical method of Bradford Hill (1955).

The mortality in relation to retinal grading and age is shown in Table V. Since that table takes no account of duration of observation from the time of acceptance, this must be considered in relation to Table VI, which

TABLE VI.—Average Duration of Life in Patients Who Died and Average Duration of Period of Observation of Patients Who Survived (7 Patients of Uncertain Retinal Grading Excluded, Pure Controls and Changed Category Controls Both Included)

	Grade 1		Grade 2		Grade 3		Grade 4	
	Died	Surv.	Died	Surv.	Died	Surv.	Died	Surv.
Controls:								
No. of patients	3	17	43	45	18	7	13	3
Average No. of months of observation	14.0	57.7	27.6	54.7	19.0	67.3	3.1	37.0
Treated:								
No. of patients	5	68	61	181	48	71	39	21
Average No. of months of observation	31.6	51.1	29.6	54.9	25.0	51.1	26.7	56.2

shows the average duration of life in patients who died, and the average period of observation of the patients who survived in treated and control series, according to their fundal grading.

Grade 4 Cases.—It can be seen that the mortality in retinal grade 4 cases was obviously diminished. The greater duration at risk of the treated patients lends

further significance to this observation. Of 30 grade 4 patients in the treated series, 14 had survived five years. No grade IV patient in the control series survived as long as five years. The survival curves illustrated in Charts 1 and 2 show clearly the improved prognosis in grade 4 cases with treatment. In Chart 2 the results in treated patients are compared with controls who had no previous treatment. In Chart 1 the controls include a group of patients who stopped treatment against advice. Their control period is dated from the cessation of treatment. The results are the same in the two groups of controls. The treated series included eight patients admitted in a terminal state who were given treatment as a last resort. Furthermore, it includes others with considerable impairment of renal function, which also must have unfavourably influenced the mortality. Seven patients, in addition to the above, had non-protein nitrogen levels over 60 mg./100 ml. at the beginning of treatment.

Grade 3 Cases.—Among cases with grade 3 retinopathy, comparing the treated with the whole series of grade 3 control cases, there is again an apparent lessening in mortality (Tables V and VI; Chart 3). However, when compared with only those control cases in which there had been no prior treatment (Chart 4), the difference is not obvious, and, in fact, results with grade 3 patients have been apparently less satisfactory than with grade 4 cases. Nevertheless, there is a suggestion that, with improvement in methods of treatment, the outlook for grade 3 patients might also improve. Whereas at the end of the first four years, 1950–3, we had 40% survivors, 60% survived the four-year period 1954–7. During the latter period, grade 3 patients have been regarded therapeutically as seriously as grade 4. The Keith, Wagener, and Barker (1939) series of grade 3 controls showed a 20% survival at four years.

Grade 2 Cases.—Of perhaps greatest interest was the comparison between treated and control patients in grade 2. As shown in Table VI, the average exposure to risk among the surviving patients was 54.9 months in the treated series and 54.7 months in the controls. For the patients who died, it was 29.6 for treated patients and 27.6 for controls. The equivalence of the periods of exposure to risk for grade 2 treated and control patients makes it possible to compare the grade 2 figures in Tables V and VI directly. There were 43 deaths among 88 controls (48.9%) and 61 deaths among 242 treated patients

TABLE V.—Mortality in Relation to Retinal Grading and Age (male and female)

Age*	Grade 1		Grade 2		Grade 3		Grade 4		Uncertain Grade		All Grades Combined	
	Died	Survived	Died	Survived	Died	Survived	Died	Survived	Died	Survived	Died	Survived
Controls												
70+	0	1	5	4	0	0	0	0	0	0	5	5
60–69	0	1	11	10	6	4	1	0	5	1	23	16
50–59	1	7	17	21	6	3	3	3	0	0	27	34
40–49	1	5	7	8	6	0	5	0	0	1	19	14
30–39	1	1	3	2	0	0	3	0	0	0	7	3
20–29	0	2	0	0	0	0	1	0	0	0	1	2
–20	0	0	0	0	0	0	0	0	0	0	0	0
Total	3 (15%)	17	43 (49%)	45	18 (72%)	7	13 (81%)	3	5	2	82	74
Treated												
70+	0	1	2	2	3	1	0	0	0	0	5	4
60–69	1	10	22	38	7	17	2	5	0	1	32	71
50–59	2	21	19	71	19	25	13	4	0	1	53	122
40–49	1	20	13	55	11	17	15	7	0	0	40	99
30–39	1	10	3	14	6	10	7	3	0	0	17	37
20–29	0	5	2	1	1	1	1	1	1	0	5	8
–20	0	1	0	0	1	0	1	1	0	0	2	2
Total	5 (7%)	68	61 (25%)	181	48 (40%)	71	39 (65%)	21	1	2	154	343

* Age when investigated and accepted either for treatment or as a control.

(25.2%). In each of the five decades where a comparison can be made the mortality was greater in the control group, but the number of patients was only sufficient to make the differences statistically significant in the decade 50-59 ($0.02 > P > 0.01$). When, however, all ages from 30 to 69 are combined, it is seen that 38 of 79 controls and 57 out of 235 treated patients died. The overall decrease in mortality with hypotensive therapy in grade 2 is therefore highly significant ($P < 0.001$).

Grade 1 Cases.—In grade 1 patients the number of deaths does not justify a comparison between the results in treated patients and those in controls. Out of 73 treated patients 5 (6.8%) died as against 3 out of 20 (15%) controls.

Effect of Omitting Cases with Prior Treatment

The question of whether it is justifiable to include as controls patients who abandoned treatment even after a very short time (changed category controls) is of some importance. In such cases the control period was counted as starting from the date of abandoning treatment. These cases, therefore, have had several months' longer exposure to hypertension since diagnosis than the treated cases. In other respects there is no suggestion that they were significantly different in severity, and in grade 2 most patients have been followed for several years after they abandoned treatment. It will be seen in Charts 1 and 2 that the inclusion of changed category controls in Chart 1 makes no appreciable difference to the control survival curve for grade 4 patients. There is a slightly better survival during the control period for females who had a period of treatment before abandoning it (changed category controls) than for females who had no treatment. In grade 3 there is a considerable difference between pure and changed category controls, and the shapes of the curves are different. In years one to three there is very little difference between the treated grade 3 patients and the pure controls, whereas when changed category controls are included a difference in survival is apparent. From the fourth to the eighth year a better survival in grade 3 treated patients than in controls is apparent in males and females whether all controls (Chart 3) or only pure controls (Chart 4) are used as the basis for comparison.

Although there is an indication of improved survival in grade 3 patients on treatment, we are insufficiently confident of this group of controls to express an opinion on the extent to which this has taken place. It is of interest, however, that our complete series of controls corresponds approximately with the Keith, Wagener, and Barker (1939) series of grade 3 controls.

In Charts 5 and 6 it can be seen that at six years among the males there were 21% survivors in the pure grade 2 controls and 29% when changed category controls are included. Among the females at six years there were 55% survivors among the pure controls and 46% among the changed category controls.

In either case, as is shown in the next section, the improvement in the treated grade 2 group is highly significant ($P < 0.001$) whether all or only pure controls are used for comparison.

Special Consideration of Grade 2 Patients

There are enough patients in this group to make possible a statistical comparison between the treated and the control series. The age difference between the

overall ages of treated and control series is obviated by considering only patients in the age groups 30-69. In this age range (males and females) there were 43 controls without an initial period of treatment, of whom 21 died; and 224 treated, of whom 51 died, a difference which is statistically significant ($P < 0.001$). This confirms a trend suggested in the early years of treatment (Smirk, 1954), when the difference in mortality had not achieved significance ($0.10 > P > 0.05$).

A method by which it is possible to take into consideration all the important points of difference between the two series has been employed to make an even more precise analysis of the differences between the prognosis for grade 2 cases in the two series. This has been done by calculating the number of life-years lost by the controls as compared with treated patients during the period under observation. These have been expressed as percentages of the number of life-years during which the treated patients and controls have been under observation. Thus five persons under observation for five years represents 25 possible life-years; if two die at three years they will each have lost two life-years, a total loss of four life-years, which as a percentage of 25 is 16% loss.

The results are set out for females in Table VII. The number of controls in males is insufficient to justify such detailed analysis but provides strong supporting

TABLE VII.—*Survival Times of Grade 2 Females (Including Controls who Changed Category)—Corrected to Same Exposure to Risk in Each Decade*

Group	Age	Total No.	Died	Actual Months Survived		Possible Months Survived		Actual as % of Possible
				Total	Av.	Total	Av.	
Treated	70+	3	1	110	36.7	177	59.0	62.2
	60-69	37	13	1,637	44.2	1,985	53.6	82.4
	50-59	57	11	3,524	61.8	3,926	68.9	89.7
	40-49	44	6	2,795	63.5	3,115	70.8	89.7
	30-39	12	0	972	81.0	972	81.0	100.0
	20-29	1	0	20	20.0	20	20.0	100.0
	—20	0	0	—	—	—	—	—
Control	70+	9	5	353	39.2	531	59.0	66.5
	60-69	18	9	656	36.4	966	53.6	67.8
	50-59	28	12	1,396	49.8	1,928	68.9	72.4
	40-49	13	5	653	50.2	921	70.8	70.9
	30-39	5	3	267	53.4	405	81.0	65.9
	20-29	0	0	—	—	—	—	—
	—20	0	0	—	—	—	—	—
Treated	30-69	150	30	8,928	59.5	9,998	66.6	89.3
Control	30-69	64	29	2,972	46.4	4,220	65.9	70.4

evidence. In this analysis both series of Grade 2 controls are considered together because there was no significant difference in the mortality experience of the two series. In each decade any differences in the period of exposure to risk of treated and control patients have been equalized by extending the period of study (designated "possible months survived") in Table VII of either the treated or the control group until the average period of exposure to risk was the same. Thus, for example, in the age-group 50-59 in females at December, 1958, the average exposure to risk for controls was 68.9 months and for treated patients 59.1 months. In order to equalize the period of exposure to risk we recorded our observations on the treated group up till October, 1959, and added an additional period of 6.7 months' observation to the treated group. (In this way we equalized the duration of exposure to risk of controls and treated in each decade.)

In this carefully matched series of grade 2 female patients aged 30 to 69 years there were 30 deaths among 150 treated patients and 29 among 64 controls (pure and

mixed), a difference which is highly significant ($P<0.001$). It can be seen that in all decades there is a consistent improvement amongst the treated cases, although the numbers in several of the control decades were deficient.

Combining results for the decades 30–69, the survival as a percentage of possible years under observation was 89.3 for those treated, and 70.4 for controls. That is to say, the loss of life-years as a percentage of possible life-years is 10.7% in treated patients and 29.6% in controls.

In males the controls were few in number, but the mortality was treated 20.9, controls 60.4.

Mortality in Grade 2, Excluding Cases of Hypertensive Heart Failure

The improvement in prognosis brought by hypotensive treatment in cases presenting with cardiac failure has already been established (Smirk, Hamilton, Doyle, and McQueen, 1958). It is therefore important to know whether the improvement in Grade 2 patients was due solely to the improved outlook of those presenting with cardiac failure. We have therefore made an analysis in which all patients (male and female aged 30–69) presenting initially with congestive failure or paroxysmal dyspnoea of cardiac origin are removed from both the treated and the control groups. With these deductions, our results show that 33 died out of 70 controls (47.1%) (grade 2 members of complete control series without cardiac failure at presentation) as against 35 out of 183 treated (19.1%). The improvement with hypotensive treatment in the outlook of grade 2 patients is influenced by, but does not depend upon, the improved outlook of the cases of heart failure ($P<0.001$). The improvement is also highly significant ($P<0.001$) when only controls without an antecedent period of treatment are used.

Hypotensive therapy, however, greatly reduces the incidence of paroxysmal dyspnoea and congestive failure in a hypertensive clinic population: it acts preventively to reduce the subsequent incidence in patients who did not exhibit heart failure before hypotensive treatment started. A further analysis has been made, therefore, in which all patients dying from hypertensive heart failure are removed from both groups. When this correction is made, deaths from causes other than heart failure accounted for 26 out of 67 (38.8%) grade 2 control patients of the complete control series as against 47 out of 225 (20.9%) patients who received treatment. Evidently extension of life in treated grade 2 patients is not solely dependent upon the treatment or prevention of heart failure ($0.01>P>0.001$).

Effect of Treatment on Causes of Death in Arterial Hypertension

Reference has been made in an earlier communication (Smirk, 1957) to the alteration in the pattern of mortality which has taken place as the result of hypotensive therapy. Causes of death are classified in Table VIII, which sets out the proportion of deaths from cardiac failure, coronary disease, cerebral vascular accident, uraemia, and other causes which took place in the years 1950–8, inclusive.

The fractions refer to those instances in which more than one cause operated. For example, if a patient with no previous indication of heart failure develops a cardiac infarction and not long afterwards congestive

TABLE VIII.—*Effect of Treatment on Causes of Death in Arterial Hypertension*

	Treated Patients		Controls*	
	No. of Deaths	Percentage of Total Treated Deaths	No. of Deaths	Percentage of Total Control Deaths
Cardiac failure ..	19½	12.7	19	23.2
Coronary ..	29½	19.2	14	17.1
Cerebral vascular accident ..	51	33.1	32½	39.6
Uraemia ..	31½	20.5	10	12.2
Other ..	22½	14.6	6½	7.9
Totals ..	154		82	

* Including deaths amongst all control patients.

TABLE IX.—*Deaths from Various Causes as Percentages of the Patients at Risk*

	Treated Patients (497)		Controls (156)	
	No. of Deaths	Percentage of Treated Patients	No. of Deaths	Percentage of Control Patients
Cardiac failure ..	19½	3.9	19	12.2
Coronary ..	29½	5.9	14	9.0
Cerebral vascular accident ..	51	10.3	32½	20.8
Uraemia ..	31½	6.3	10	6.4
Other ..	22½	4.5	6½	4.1

heart failure, and dies, the cause of death will be recorded as coronary ½, heart failure ½. A patient dying from pneumonia would be counted solely as a death from pneumonia if infection was the only obvious cause of death; but if such a patient, while in a deteriorated stage from pneumonia, developed uraemia, thus indicating that the hypertensive disorder had contributed to the fatality, then the cause of death would be recorded as pneumonia ½, uraemia ½.

Table IX shows the deaths from various causes expressed as percentages of the numbers of treated and control patients at risk. It will be seen that in treated patients deaths from heart failure are a third of those in controls and cerebral vascular accidents are a half of those in controls.

Amongst our treated cases there have been five deaths from dissecting aneurysms. Among control patients there has been no death from dissecting aneurysm but two from non-dissecting (arteriosclerotic aneurysm).

Discussion

It is generally accepted now that patients with grade 3 or grade 4 (Keith, Wagener, Barker) retinopathy and patients with paroxysmal dyspnoea of cardiac origin or with general hypertensive heart failure should be treated by reduction of the blood-pressure. Our results in grade 2 patients, in whom retinal changes are confined to changes in small arterial blood-vessels, now allow some conclusions to be drawn concerning the desirability of hypotensive therapy in these patients.

This paper summarizes the results of the first eight out of ten years of our experience with hypotensive therapy, in which an attempt has been made to maintain the blood-pressure as near to normal as is practicable. In both treated and untreated patients the mortality is higher in the first year than in subsequent years. This is because the attendance at hospital is often for some substantial illness and those who survive the first year after reference to hospital have a better chance of several years' survival. Previous reports from this clinic described a considerable decrease with effective

hypotensive therapy in the mortality of retinal grade 4 (malignant hypertension), and some decrease in retinal grade 3 patients (Smirk, 1954, 1957). Several contributors to the First Hahnemann Symposium on Hypertension edited by Moyer (1959) related corresponding experiences with severe hypertensives.

The increased experience of a longer period of treatment has borne out earlier observations of the value of hypotensive drug therapy in grade 3 and grade 4 hypertension. There is now evidence also that improvement in survival is shown by patients with hypertension of grade 2 severity.

Previous surveys of results from hypotensive therapy have been concerned more especially with the severer grades of hypertension, and improvement has been claimed by almost all observers despite differing regimens of treatment. Barnett (1956) obtained a survival rate at twelve months of 72% in patients with grade 4 hypertension, but only 5 out of 32 grade 4 patients survived to four years. Perry and Schroeder (1958) found a significantly lower mortality in treated than in untreated patients. Dustan, Schneckloff, Corcoran, and Page (1958) reported their follow-up of 81 cases of malignant hypertension treated for up to seven years with various combinations of ganglion-blocking drugs, hydralazine, and reserpine. In this series the survival rate at three years was 52%, at six years 25%. Patients who survived for less than three months were excluded from the analysis.

The relationship between the level of diastolic blood-pressure while on treatment with ganglion-blocking drugs and the incidence of complications was referred to by Newman and Robertson (1959). A clear correlation was shown for patients with grade 3 and grade 4 hypertension, both morbidity and mortality being reduced by effective treatment.

The most recent report of treatment in malignant hypertension has been that of Harington, Kincaid-Smith, and McMichael (1959), whose 82 cases included 45 with blood urea over 60 mg./100 ml. Three-year survival for all treated patients was 30% and six-year survival 18%. When patients presenting with a blood urea over 60 mg./100 ml. were excluded, the figures were 45% survival at three years and 30% at six years. Patients in terminal state were excluded from the analysis.

Particular attention has been devoted in this paper to a generally milder class of case—namely, the retinal grade 2 patients. The mortality of retinal grade 2 patients is also reduced considerably by hypotensive therapy as compared with controls. Controls (males plus females aged 30–69 years) to which it is difficult to find any objection are 43 in number and are grade 2 patients we desired to treat but who, when the nature of the treatment was explained to them, declined it. With these controls only the lower mortality of treated cases is significant ($P<0.001$). We also used as controls 36 patients who had been on hypotensive treatment but abandoned this. There is no significant difference between the mortalities of the two groups of grade 2 controls. With both groups of controls, the significance of the lower mortality in the treated group also is $P<0.001$. The percentage mortality was 48.1 in the controls and 24.3 in the treated.

It is, however, well recognized that patients with grade 2 retinopathy may have congestive heart failure and die from it. We have previously shown that hypertensive heart failure may be treated with

hypotensive therapy without any adjuvants such as digitalis or diuretics (Smirk *et al.*, 1958). It is therefore important to know if any significant trend of improvement emerges when cases presenting with heart failure are removed from the grade 2 group. Our results show that the reduced mortality in grade 2 patients remains significant when patients presenting with heart failure are removed from both control and treated groups ($P<0.001$). The difference between control and treated groups also remains significant if all patients dying from heart failure are removed from the two groups ($0.01>P>0.001$).

Taking all retinal grades together there has been a statistically significant ($0.05>P>0.02$) lessening in deaths from hypertensive heart failure (as a percentage of total deaths) among the treated patients relative to their frequency among the controls. The percentage of cerebrovascular accidents as a cause of death was also lower in the treated than in the control series, and the percentage for uraemia higher, possibly as a result of diminution in the frequency of heart failure and stroke as causes of death in patients with renal insufficiency.

When, in all retinal grades, the percentages of deaths from various causes are expressed as a percentage of the patients at risk in the two categories, the decreases in mortality are highly significant in heart failure ($P<0.001$) and cerebral vascular accidents ($P<0.001$), despite the higher proportion of severe retinal grades among the treated patients.

Although over the years since effective hypotensive treatment by pharmacological means was initiated numerous different hypotensive agents have been used, and although with experience much-improved regimes have been developed, the decreased mortality with therapy does not appear to depend upon the nature of the measures used to reduce the blood-pressure.

Summary

The results of hypotensive treatment over a period of eight years are reviewed. There were 497 patients on hypotensive therapy and 156 controls.

The improvement with treatment in the mortality of retinal grade 4 and grade 3 patients is confirmed.

There has been a highly significant ($P<0.001$) improvement in the mortality of retinal grade 2 patients, 61 deaths occurring among 242 treated grade 2 patients (all ages) as contrasted with 43 among 88 controls.

The relative loss of life-years during the eight-year period of study was nearly three times as great in grade 2 controls as in grade 2 treated patients.

Even if grade 2 patients presenting with paroxysmal dyspnoea or heart failure are excluded from both treated and control series, the improvement in the mortality is highly significant ($P<0.001$).

Taking all grades together, despite the predominance of severe retinal grades in the treated patients there was a reduction in the death rate (as a percentage of patients at risk) from heart failure ($P<0.001$) and from cerebral vascular accidents ($P<0.001$) in the patients on hypotensive therapy.

The decreased mortality does not appear to depend upon which particular measures are used to reduce the blood-pressure. The consistent aim of our hypotensive therapy has been to reduce the blood-pressure level of hypertensive patients to as near normal as practicable.

No claim is made for the efficacy of less substantial reductions of the blood-pressure.

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REFERENCES

- Barnett, A. J. (1956). *Aust. Ann. Med.*, 5, 274.
 Dustan, H. P., Schneekloth, R. E., Corcoran, A. C., and Page, I. H. (1958). *Circulation*, 18, 644.
 Harington, M., Kincaid-Smith, P., and McMichael, J. (1959). *Brit. med. J.*, 2, 969.
 Hill, A. B. (1955). *Principles of Medical Statistics*, 6th ed. Lancet, London.
 Keith, N. M., Wagener, H. P., and Barker, N. W. (1939). *Amer. J. med. Sci.*, 197, 332.
 Moyer, J. H. (1959). *Hypertension* (The First Hahnemann Symposium on Hypertensive Disease). Saunders, Philadelphia and London.
 Newman, M. J. D., and Robertson, J. I. S. (1959). *Brit. med. J.*, 1, 1368.
 Perry, H. M., jun., and Schroeder, H. A. (1958). *Arch. intern. Med.*, 102, 418.
 Smirk, F. H. (1954). *Brit. med. J.*, 1, 717.
 — (1957). *High Arterial Pressure*. Blackwell, Oxford.
 — Hamilton, M., Doyle, A. E., and McQueen, E. G. (1958). *Amer. J. Cardiol.*, 1, 143.

COMPARATIVE TUBERCULIN-TESTING OF HUMAN SUBJECTS

A METHOD OF DIFFERENTIATING THE TYPE OF VIRULENT MYCOBACTERIAL INFECTION

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The successful discovery of the source of tuberculous infection by single or repeated tuberculin-testing of adults (Gedde-Dahl, 1952) and schoolchildren (Tattersall, 1952; MacDougall *et al.*, 1953; Davies, 1955) has been reported. Persistent attempts over the last six years to repeat this technique in Ipswich and East Suffolk resulted in the tracing of the source of infection in about a fifth of the children tuberculin-positive at their first test, and in a third of those converting their tuberculin test (van Zwanenberg, 1960). It was suspected that much of the infection unaccounted for might be due to milk infection with the bovine type of *Mycobacterium tuberculosis*. In such circumstances a simple method of comparative tuberculin-testing as is used by veterinary surgeons to determine the type of mycobacterial infection in cattle would be of great value. Testing simultaneously with avian and mammalian tuberculin they are able to differentiate virulent mycobacterial infection from tuberculin hypersensitivity due to other causes (Francis, 1958). In his report on the preparation of Weybridge P.P.D., Green (1946) showed that guinea-pigs hypersensitized to different strains of *Mycobacterium* gave the largest reactions to the homologous P.P.D. tuberculin.

Until recently there have been very few reports on comparative tuberculin-testing of human subjects. Avian and human tuberculin have been used by Edwards *et al.* (1953) and by Kuper (1958) in an attempt to differentiate between hypersensitivity due to virulent *Mycobacterium tuberculosis* and "non-tuberculous" hypersensitivity. The work of Enell (1955) and Lorber (1957)

has shown that reactions to B.C.G. tuberculin are larger than those to human P.P.D. in B.C.G.-vaccinated persons. More recently Edwards and Palmer (1958) have shown that patients harbouring anonymous (Battey) *Mycobacterium tuberculosis* give larger reactions to P.P.D. prepared from that organism than to P.P.D.-S. (human).

Without knowledge of this recent work, we carried out some preliminary tuberculin-testing of adults and children with bovine and human P.P.D. in 1957. The result suggested that comparative testing might be of value in indicating the type of infecting *Mycobacterium*. This paper describes the results of the subsequent tuberculin-testing of schoolchildren in East Suffolk County and Norwich with human and bovine P.P.D. and relates the findings to the known facts concerning tuberculous disease and infection in each district.

Population Studied

The subjects in this survey were schoolchildren aged 5 to 18 living in six districts in East Suffolk County and one group from the City of Norwich. The schoolchildren from 5 to 11 years old live in or near the town or village in which the school is situated. Older children come from a wider area surrounding the school. In six districts over 80% of the school population accepted and completed the tests. In Hartismere only 78% of the total school population completed the tests; 12% attend schools outside its boundaries and have not as yet been tested.

East Suffolk is predominantly rural. The industry and occupations are mainly concerned with farming. Of the seven districts covered by this investigation, only Hartismere (16,940 pop.) is entirely rural and has no occupation other than farming, most of which is arable, although in the north along the Waveney Valley there are a number of dairy farms. Four of the districts—Woodbridge (5,620 pop.), Bungay (3,610 pop.), Beccles (7,000 pop.), and Stowmarket (7,580 pop.)—are small market towns surrounded by arable and mixed farming areas. In Beccles there is a printing works employing 1,000, Stowmarket has a paint factory employing 1,000 and an iron foundry employing 700. Felixstowe is a residential coastal resort with a large number of summer visitors and no factories. Norwich City (118,000 pop.) is the county town of Norfolk. It is a large trading centre with mixed light and heavy industry.

Method and Materials

All children received two Heaf multiple-puncture tuberculin tests. Bovine P.P.D. 1 mg./ml. (Weybridge) was applied to the right forearm, and human P.P.D. 2 mg./ml. (Weybridge) to the left forearm. This human P.P.D. is the standard preparation issued by the Weybridge laboratory of the Ministry of Agriculture, Fisheries and Food for the routine tuberculin-testing of cattle and for the commercial dispensing and dilution, and is issued by the Ministry of Health to local authorities for the tuberculin-testing of schoolchildren. It is prepared from three strains of human-type *Mycobacterium* designated C, D.T., and P.N. that have been maintained separately in the laboratory for a number of years (Green, 1946). The bovine P.P.D. is prepared in the same laboratory from a single strain "OTTO" (A. B. Paterson, 1960, personal communication). It is issued in 1 mg./ml. strength for research and experimental work only. The relative strength of the tuberculins is that arrived at by Green (1946) as a