TABLE C.—*Actual and Standardized Numbers of Suicides by Months in Certain Periods in England and Wales and in Australia*

Month	England and Wales												Australia			
	1921-9				1930-9				1940-8				1930-9			
	Actual No.		Standardized No.		Actual No.		Standardized No.		Actual No.		Standardized No.		Actual No.		Standardized No.	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Jan. . .	2,234	823	2,193	808	3,058	1,400	3,002	1,374	1,751	1,005	1,720	987	591	147	580	144
Feb. . .	2,009	857	2,167	924	2,767	1,239	2,986	1,337	1,729	991	1,858	1,065	537	139	580	150
March . .	2,396	1,006	2,352	988	3,246	1,478	3,187	1,451	2,096	1,120	2,058	1,198	571	135	561	133
April . .	2,494	961	2,530	975	3,325	1,529	3,373	1,551	2,075	1,175	2,106	1,192	475	99	482	100
May . .	2,542	1,057	2,496	1,038	3,374	1,507	3,312	1,479	1,977	1,207	1,942	1,185	520	127	511	125
June . .	2,475	1,045	2,511	1,060	3,262	1,509	3,309	1,531	2,140	1,186	2,172	1,204	445	114	451	116
July . .	2,570	1,053	2,523	1,034	3,180	1,420	3,122	1,394	1,960	1,256	1,925	1,233	522	135	512	133
Aug. . .	2,287	915	2,245	898	3,015	1,321	2,960	1,297	1,759	1,084	1,727	1,065	487	138	478	135
Sept. . .	2,161	885	2,192	898	2,911	1,312	2,953	1,331	1,760	1,038	1,786	1,053	558	134	566	136
Oct. . .	2,145	896	2,106	880	2,718	1,362	2,668	1,337	1,654	1,061	1,624	1,042	546	174	536	171
Nov. . .	1,979	830	2,008	842	2,621	1,341	2,659	1,360	1,613	1,047	1,637	1,063	550	135	558	137
Dec. . .	2,140	891	2,101	875	2,728	1,354	2,678	1,329	1,740	1,118	1,709	1,098	524	164	514	161

The standardized numbers were computed to four decimal places for the graphs and calculations given in this paper.

ANTIHISTAMINE TREATMENT OF ACUTE NEPHRITIS

BY

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In almost every case of acute nephritis a history can be obtained of a bacterial, usually a streptococcal, infection which precedes the nephritis by between one and three weeks; it was this uniform association, and the characteristic time interval, which gave rise to the idea that immunity responses were involved in the pathogenesis of the disease—an aetiological hypothesis which is now widely accepted. The known mediation of histamine or a histamine-like substance as a final common path in the production of a variety of hypersensitivity phenomena made it likely that sooner or later a trial would be given to one of the recently developed antihistamine drugs in the treatment of acute nephritis.

The theoretical basis of such a treatment is tenuous, consisting as it does merely in the observed association mentioned above; and a consideration of the characteristics of the disease will suggest that the interpretation of the results in a fairly short series of cases is likely to be very difficult.

Acute nephritis is known to have, on the whole, a very good prognosis, but nevertheless to follow a widely variable course. There are very few cases which, properly managed, will suffer permanent impairment of renal function or develop progressive disease, though the exact effect of such management is not clearly known: it follows that even if a treatment were found which would absolutely prevent such serious consequences a very long series would have to be studied to prove that this was the case. There are only two ways in which this difficulty might theoretically be overcome.

First, if it were possible to define clearly on admission which cases were likely so to progress. Unfortunately this is not possible, nor has it ever been shown that there is a strong correlation between the severity of the disease at its inception, however measured, and the long-term prognosis.

Secondly, if the treatment under trial were to give dramatic and sudden relief of the symptomatology of

the disease. Even if this were to occur the effect upon long-term prognosis would not be clearly proved until a large series had been followed up, although the probability of such effect would be strong enough to justify the optimistic use of the treatment.

Craig, Clark, and Chalmers (1949) reported their experience in the use of mepyramine maleate ("anthisan") in the treatment of a series of cases. The average duration of the disease in their treated series was two to three weeks, and in the series of untreated cases, with which it was compared, about four months. This result was encouraging, but the work suffered, as the authors pointed out, from two defects: first, there were only eight cases in each series; and, secondly, the treated and the control cases occurred in different years, and the series could not therefore be regarded as adequately controlled.

Present Investigation

After the publication of their article it was decided to carry out a carefully controlled trial of mepyramine maleate in the treatment of acute nephritis at the Hospital for Sick Children.* The arrangements for the trial were as follows.

All cases of acute nephritis—Ellis (1942) Type 1—admitted to the hospital between May 1949 and May 1950 were included in the series. Each case on admission was allotted a serial number. Odd numbers were treated with mepyramine maleate; even numbers were controls. The following records were made in all cases; (a) a 24-hour specimen of urine was collected whenever possible for each of the first few days; (b) daily blood-pressure readings were taken until stable and normal; (c) daily blood-urea levels were estimated until they were stable and normal; (d) daily fluid intake was measured for the first few days; (e) daily weight was recorded until stable; (f) the E.S.R. was estimated on admission and weekly until normal; and (g) when gross haematuria had ceased, weekly Addis counts took the place of the daily urinary investigation until discharge, after which they were performed monthly and subsequently at longer intervals.

Mepyramine maleate was given to alternate cases for ten days in the following dosage:—*Children under 3*: 300 mg. daily in divided six-hourly dosage; *children over 3*: 600 mg. daily in divided six-hourly dosage.

*The inefficacy of mepyramine in a series of similar length has since been reported by Thomson (1949).

A third of this dosage was given initially; it was then built up rapidly to the full dosage in a day or two. No signs of toxicity were noted in any child.

All cases, both in the control and in the treated series, were given penicillin intramuscularly in normal therapeutic dosage for five days, in order that all should be on the same footing so far as the treatment of infection was concerned. In order further to standardize management, the following diet was given in all cases: For the first two or three days glucose and fruit juice only. For the next day or two a low-protein diet was given, and was built up to a diet of normal protein intake—that is, about 1 g. per pound body weight a day—by the fifth or sixth day, but with no added salt until the urinary output had become normal. The fluid intake until diuresis had occurred (in those cases showing evidence of fluid retention) was restricted to 15 ml. per pound body weight a day—that is, estimated non-urinary loss—plus the previous 24-hours' urinary output.

The children were kept in bed in this hospital, or in the later stages at the country branch hospital, until the blood pressure, blood urea, and urinary output were normal, and until the Addis count and E.S.R. were approaching the upper limits of normality. After discharge the cases were all examined once a month in a special follow-up clinic.

Thirty-six consecutive cases were admitted to the series, but of these three were withdrawn: a relapsing case first seen in a relapse; a case in which mepyramine was given, owing to a misunderstanding, for three days only; and a fatal case of pneumococcal meningitis with a secondary nephritis. There remain, therefore, 33 cases for analysis—16 mepyramine and 17 control cases.

The comparability of the two series as they arose by automatic alternate selection of cases is studied in Table I. It will be seen that the two series were in

TABLE I.—Comparability of the Two Series on Admission

	No.	Age under 5	Sex	Oedema	Hypertension	Nitrogen Retention	Albuminuria	Haematuria	Raised E.S.R.
Mepyramine	16	5	6M 10F	9	6	5	14	16	16
Control ..	17	8	6M 11F	12	10	7	17	16	15
Total ..	33	13	12M 21F	21	16	12	31	32	31

fact reasonably similar, both as regards sex and age distribution and in terms of the criteria of severity on admission; that is to say, the frequency of oedema, hypertension, and nitrogen retention.

In Table II the following items have been analysed in terms of the number of days' duration of each abnormal finding in each case. The length of history on admission is also recorded.

Oedema.—This is recorded in terms of the number of days before stable weight is reached.

Diastolic Hypertension.—No arbitrary upper limit of normality was set: the time is recorded at which the diastolic pressure in each case reached a stable level within the gross limits of normality. Difficult borderline cases were expected, but none occurred: in every case recorded as hypertensive the diastolic pressure was above 95 mm. Hg on admission, and in each of these (except Case 6, in whom the disease is still active) the stable level eventually reached was below 80 mm. Hg.

TABLE II

Serial No.	Sex	Age (Years)	Length of History (Days)	Duration in Days of Each Abnormal Sign (Day of Admission = 0)						Total Duration of Activity (Days)
				Oedema	Diastolic Hypertension	Nitrogen Retention	Albuminuria	Red Cell Excretion in Excess of 5 Million per Diem	Raised E. S. R.	
Mepyramine Malcate Series										
1	M	4	4	—	—	11	20	82	70	82
3	F	7	7	3	—	—	10	11	18	18
9	F	7	1	8	—	—	8	15	34	34
11	F	9	5	—	30	8	67	130	75	130
13	M	10	7	5	10	6	30	70	53	70
15	F	10	21	6	7	—	42	102	75	102
17	F	2	2	—	—	—	—	21	38	38
19	F	7	7	4	5	—	3	55	20	55
21	F	7	10	7	—	—	—	40	14	40
23	M	4	1	—	—	7	8	55	105	105
25	M	6	7	—	3	—	10	25	10	25
27	M	2	3	—	—	—	12	70	12	70
29	F	10	6	8	8	—	28	150	48	150
31	F	6	5	3	—	—	8	56	60	60
33	M	2	0	—	—	—	1	8	10	10
35	F	6	1	10	—	6	14	80	86	86
Mean							16	62	45	67
* Control Series										
2	M	2	7	3	—	1	13	43	6	43
6	M	12	7	14	180+	30	180+	180+	180+	180+
8	M	5	1	4	—	—	2	7	*	7
10	F	6	14	10	9	—	7	14	19	19
12	F	3	2	—	—	—	7	—	5	5
14	F	8	4	3	9	1	5	21	—	21
16	F	4	6	—	—	8	15	105	35	105
18	M	3	7	10	7	7	22	55	50	55
20	M	6	8	3	8	—	1	50	45	50
22	F	7	1	—	3	—	2	60	60	60
24	F	4	1	4	—	—	2	15	—	15
26	F	1	5	11	10	—	6	28	12	28
28	F	10	6	5	5	—	6	50	45	50
30	F	5	4	—	—	—	2	8	9	9
32	F	6	5	6	20	—	9	62	*	62
34	F	4	21	4	4	6	9	76	40	76
36	M	3	7	—	—	8	8	90	96	96
Mean							17	52	40	52

* In Cases 8 and 32 the significance of the Addis count was vitiated by the presence of other infection.

Raised Blood Urea.—40 mg. per 100 ml. is taken as the upper limit of normality.

Proteinuria.—20 mg. per 100 ml. is taken as the upper limit of normality.

Addis Count.—The time in days at which the red-cell excretion falls below 5,000,000 cells in 24 hours is recorded. The 5,000,000 level is the lowest which it is practicable to use for the comparative assessment of progress; it is uncommon, except in a clear relapse, for the count to rise above 5,000,000 once it has fallen below it, whereas there is often an oscillation around the 1,000,000 level for several weeks. For the final assessment of inactivity, however, the 1,000,000 level is taken, and all cases recorded as inactive showed red-cell excretions below 1,000,000.

Erythrocyte Sedimentation Rate.—The time in days is recorded at which the E.S.R. falls below 15 mm. in one hour. In the final assessment of inactivity, however, the level of 10 mm. in one hour was taken. The reasons for the use of the higher level in the initial assessment are similar to those governing the selection of the 5,000,000 level for the Addis count.

Total Duration of Activity.—In this column is recorded the number of days until normality is reached by all the above criteria.

Results

All cases but one have completely resolved according to all the criteria used within periods varying between 5 and 150 days after admission. The only case still active is a 12-year-old boy who is still hypertensive and

has a raised Addis count and E.S.R. and passes 300 mg. of albumin per 100 ml. of urine 14 months after admission. This child is a member of the control

TABLE III.—Showing the Number of Cases Reaching Normality by All Criteria During each Month After Admission

Days:	1-30	31-60	61-90	91-120	121-150	Over 150
Mepyramine (16 cases)	3	5	4	2	2	—
Control (17 cases)	7	5	2	2	—	One case still active
Whole series (33 cases)	10	10	6	4	2	One case still active

series. It is clearly impossible to judge the effect of mepyramine maleate on the long-term prognosis in this series, in which only one case has failed to resolve completely. The following analysis therefore refers only to the experience of the first six months in each case, and for the purpose of the statistical analysis the still active case has been allotted the full period of six months. Follow-up periods range between six and eighteen months.

The mean period taken to return to normality in the mepyramine series is 67 days, whereas in the control series it is 52 days. If, in addition, the various criteria of cure are analysed separately it will be seen that the cases in the control series did consistently better than those in the mepyramine series; the mean times taken to achieve normality in respect of Addis count and E.S.R. were longer in the treated than in the control series. The first impression therefore is that mepyramine maleate is deleterious.

This difference is not, however, significant. As is shown in Table IV, the value of "t" is only 1.03, whereas it would have to be 2.04 in order to attain the lowest conventional level of significance—that is, to show that the difference was such as would arise by chance not more than once in every 20 such trials.

Further Analysis of the Series

The criticism may be made, after a study of Table II, that the series is heavily diluted with cases which were very mild on admission. Before the trial began it was decided that every case diagnosed clinically on admission as acute nephritis (Ellis Type 1) must enter the series in order to avoid both bias and the possible criticism of bias in the acceptance of cases for either half of the series. Furthermore, if any exact laboratory data were to be used either in diagnosis or in the definition of severity, there would be inevitable delay after admission before the cases could enter the series; this delay might affect the two halves of the series differently, and treatment of the mepyramine cases would be delayed.

It was also recognized that it would be perfectly easy, should it seem desirable, to eliminate retrospectively cases of extreme mildness, provided that the criteria for so doing were clearly defined and did not depend upon any observations or measurements taken after treatment had begun. But in view of the lack of correlation between severity and long-term prognosis in this disease, to which reference has already been made, there seems to be no reason to exclude any case from the series. A separate analysis has, however, been made of the series formed of cases which passed one or another criterion of severity on admission; in Table IV the experience of cases presenting with

TABLE IV.—Statistical Analysis

		No. of Cases	Mean Duration (Days)	Difference Between Means (Days)	“t” test		
					Arithmetical Series	Logarithmic Series	5% Point
(a) Whole series	Mepyramine Control	16 17	67 52	15	1.03	1.42	2.04
(b) All cases with initial oedema	Mepyramine Control	9 12	68 51	17	0.93	1.35	2.09
(c) All cases with initial hyper-tension	Mepyramine Control	6 10	89 60	29	1.19	1.29	2.15
(d) All cases with initial nitrogen retention	Mepyramine Control	5 7	95 82	13	0.49	0.92	2.23

oedema, hypertension, and nitrogen retention, respectively, is analysed. It is seen that the difference between the trial and control cases remains insignificant by whatever criterion the series is divided.

As it seems likely that a logarithmic time scale is more appropriate than an arithmetical one on which to plot a process such as recovery from tissue damage, the above calculations have been duplicated, using not the actual numbers of days taken to return to normality, but the logarithms of these numbers (Table IV): although Student's "t" values are then considerably higher than in the arithmetical series, nevertheless significance is not attained in any case.

Summary

An attempt has been made to control as many of the variables as possible in the management of a series of 33 consecutive cases of acute nephritis (Type 1 Ellis), of which alternate members were treated with an antihistamine drug for 10 days.

Cases have been followed for periods ranging between 6 and 18 months: this report refers to the first six months' experience of each case, during which period every child except one recovered completely.

The periods in days taken to return to normality by various criteria are recorded.

Analysis of the total durations of activity shows that the mepyramine cases were consistently slightly slower to resolve, but that these differences are not significant ($P=0.05$).

This study was undertaken following a report that mepyramine had proved valuable in the short-term management of acute nephritis. This finding is not confirmed.

In a short series such as this, in which every child but one recovered fully within a few weeks or months, it is not possible to study the effect of the drug upon the long-term prognosis: but, as a sound theoretical basis for the treatment is lacking, it does not appear justifiable to embark upon a necessarily lengthy and laborious investigation of this kind without a better empirical background than this study affords.

I wish to express my gratitude to the physicians and pathologists of the Hospital for Sick Children for their co-operation in this trial, and to the Research Committee of the hospital, under whose auspices the work was carried out, for permission to publish the results. I am also indebted to Dr. J. A. Fraser Roberts for advice on the statistical treatment.

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