TRIAL OF ANTISTIN IN THE COMMON COLD

BY

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Following American reports of the suppression of symptoms of the common cold by the prompt administration of antihistaminics, it was felt necessary to make a large-scale trial in the United Kingdom, adopting such controls as were practicable, in an endeavour to remove doubt concerning the efficacy or otherwise of the suggested treatment. "Antistin" (2-phenyl-benzyl-aminomethyl-imidazole hydrochloride), synthesized by Miescher, Urech, and Klaren, of Ciba, was selected as suitable for such a trial because it is an antihistaminic of which favourable reports have been published in the treatment of allergic conditions such as urticaria, angioneurotic oedema, and hay-fever, and it has a comparatively low incidence of side-effects (Meier and Bucher, 1946; Britton, 1947; Overton, 1948).

The plan of the trial was based on that of the Medical Research Council's trial of patulin in the treatment of the common cold. Their report (1944) emphasized the following points in connexion with such a trial:

1. Since there is no reason to believe that the common cold is always or even usually due to the same agent either in sporadic cases or in different epidemics, it is necessary to include a large number of patients at several widely separated places, over a period long enough to exclude the possibility that a single prevalent epidemic is being studied.

2. Since the duration of colds is not constant but varies not only between different epidemics but also between different patients in the same epidemic, there must be a satisfactory series of control cases. This can be done only by ensuring that alternate cases at each centre receive a spurious treatment which to the recipient is indistinguishable from the genuine treatment.

3. The objective signs associated with the common cold are too variable to suffice as criteria of its presence or progress. A cold manifests itself mainly by subjective symptoms, and consequently diagnosis rests mainly upon the statements of the untrained patient.

Method

The trial was carried out in eight factories and one public school. These centres, comprising a total population of over 50,000, were widely scattered throughout the country. Antistin tablets (0.1 g.) and dummy tablets of identical appearance and practically identical taste were used, the latter having the following composition: lactose, 0.085 g.; quinine sulphate, 0.005 g.; starch, 0.031 g.; talc, 0.015 g.; and gelatin, 0.004 g. (The *British Pharmacopoeia* gives the effective dose of quinine sulphate as 0.3 to 0.6 g.)

It was arranged that none of the medical staff at any of the trial centres should be informed which tablets were active and which dummy. In order further to reduce the likelihood of identification, four letters were used instead of two (Q and S being dummy, and R and T antistin). The tablets were packed in cellophane containers, each container of nine tablets bearing one of the above four letters and instructions for taking the tablets.

It was originally intended that each patient should be seen by a doctor, but in three of the smaller trial centres there was none, and in some of the remainder it was impossible for the doctor to see all patients himself. There-

fore many of the case record cards were completed by nurses or medical orderlies. Since the record was in the main simply the patient's own account of his symptoms there seemed to be no serious objection to this procedure.

So far as possible the investigation was confined to patients reporting within 24 hours of the onset of a cold. At the first examination, after recording the patient's name, occupation, etc., on a case record card, the relevant items among the following were ringed:

Duration of cold before first examination: 6, 12, 24 hours.
Nasal: Sneezing Discharge (clear, purulent) Obstruction.
Throat: Soreness Irritation Hoarseness Cough.
Head: Fullness Stiffness Headache Lacrimation.
General: Malaise Pains Feverish.

At one centre, where all cases were seen by the doctor, the presence or absence of the following physical signs was regularly recorded: pharyngitis, laryngitis, tonsillitis, and sinusitis. The above scheme is by no means free from criticism, but it appeared to serve its purpose.

Successive patients received containers of tablets marked Q, R, S, and T, and the appropriate letter was noted on the case record card. Instructions were given to take two tablets at once, and thereafter one tablet every four hours except during the night. The patient was asked to report again after 24 hours, 48 hours, and one week, and at each interview the patient's own opinion whether the cold was cured, improved, or unaffected was recorded. The number of tablets taken was also noted. Not altogether surprisingly, the request to report three times during treatment met with only very partial success. The trial ran from November, 1949, until April, 1950.

Results

Therapeutic trials were carried out in nine centres, and the records of 1,744 patients were received from these centres. The numbers were 866 in the treated group and 877 in the control group, while for one person the group was not recorded. Of the treated group 379 and of the control group 366 reported after 24 hours, 48 hours, and seven days. Records for the remaining patients who reported once or more were completed for the first day after treatment for 318 in the treated group and 344 in the control group, for the second day after treatment for 245 treated and 249 controls, but only 23 treated and 21 controls reported on the seventh day.

The method of alternative allocation to the treated and control groups gave two groups which were comparable with regard to initial symptoms. Table I shows that the

TABLE I.—Symptoms at First Examination

	Treated		Controls	
	No.	%	No.	%
Nasal:				
Sneezing	528	61.0	553	63.1
Clear discharge ..	478	55.2	469	53.5
Purulent discharge ..	83	9.6	87	9.9
Obstruction	184	21.2	201	22.9
Throat:				
Soreness	283	32.7	233	26.6
Irritation	198	22.9	198	22.6
Hoarseness	155	17.9	139	15.8
Cough	329	38.0	293	33.4
Head:				
Fullness	152	17.6	158	18.0
Stiffness	358	41.3	370	42.2
Headache	299	34.5	287	32.7
Lacrimation	98	11.3	104	11.9
General:				
Malaise	146	16.9	105	12.0
Pains	79	9.1	91	10.4
Feverish	85	9.8	87	9.9
Physical signs*:				
Pharyngitis	106	12.2	119	13.6
Laryngitis	13	1.5	9	1.0
Tonsillitis	19	2.2	15	1.7
Sinusitis	38	4.4	30	3.4

* Recorded in one factory only.

distributions of symptoms at the first examination were very similar for the two groups.

The results for the patients who reported on each of the three days are shown in Table II. On each day the proportion recovering was slightly smaller in the treated than in the control series, but none of the differences is statistically significant.

TABLE II.—Results for Patients who Reported on Each of Days 1, 2, and 7

	Day 1		Day 2		Day 7	
	Treated	Controls	Treated	Controls	Treated	Controls
Cured ..	6	9	56	68	168	163
Improved ..	208	215	213	203	121	120
No effect ..	165	142	110	95	90	83
Total ..	379	366	379	366	379	366
% cured:						
Treated ..	1.6		14.8		44.3	
Controls ..	2.5		18.6		44.5	
Difference ..	-0.9		-3.8 ± 2.7		-0.2 ± 3.6	
% cured and improved:						
Treated ..	56.5		71.0		76.3	
Controls ..	61.2		74.0		77.3	
Difference ..	-4.7 ± 3.6		-3.0 ± 3.3		-1.0 ± 3.1	

The experience of the patients with incomplete records is shown in Table III. In this group the controls also showed a statistically insignificant advantage over the treated.

TABLE III.—Results for Patients with Incomplete Records

	Day 1		Day 2	
	Treated	Controls	Treated	Controls
Cured ..	8	9	31	39
Improved ..	169	191	127	142
No effect ..	141	144	87	68
Total ..	318	344	245	249
% cured:				
Treated ..	2.5		12.7	
Controls ..	2.6		15.7	
Difference ..	-0.1		-3.0 ± 3.1	
% cured and improved:				
Treated ..	55.7		64.5	
Controls ..	58.1		72.7	
Difference ..	-2.4 ± 3.9		-8.2 ± 4.2	

No direct or indirect questions were asked concerning possible side-effects. The number of patients who had conditions which they attributed to the treatment was too small for detailed analysis, for only 14 in the treated group and 13 in the control group complained that the tablets had any adverse effects. Most of the symptoms described could in fact have been symptoms of the cold.

Conclusion

A large-scale trial of antistatin failed to show that this drug had any effect on the course of the common cold.

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EARLY CLINICAL MANIFESTATIONS OF DISSEMINATED SCLEROSIS

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The object of this investigation was to determine which clinical features of disseminated sclerosis are of most diagnostic value, with special reference to the paramount importance of early recognition. The report is based on an analysis of 389 cases of disseminated sclerosis, 79 of which were investigated in a medical ward in the Western Infirmary, Glasgow.

Although not directly concerned in this report with the aetiology of disseminated sclerosis, we would suggest, as does McAlpine (1946), that the evidence in favour of the infective nature of the disease is increasing. Such a contention is strengthened by the recent work of Steiner (1941) and of Margulis and his associates (1946). Campbell and his colleagues (1947) and Campbell (1947) re-emphasize the possible relationship between disseminated sclerosis and agricultural exposure, previously referred to by Morawitz (1904), Steiner (1918), Dreyfus (1921), Adams (1923, 1927), and Wilson (1927).

The diagnosis of disseminated sclerosis at an early stage is important from the point of view of treatment. If therapeutic measures are to be of benefit they must be employed before irreparable damage has been inflicted on the central nervous system. This will be equally true if and when the causal agent is known and specific treatment is available for its eradication. As stressed by one of us in 1923, the ideal hope for the future lies in prevention of infection of the individual by detecting the mode of transmission. Ferraro (1944) has suggested that, once the initial aetiological basis is established, additional factors, such as the development of antigens from the white or grey matter, may play a part in the progress of the disease or in its exacerbations. Bailey and Gardner (1940) have shown that antigenic substances can be derived from myelin sheaths. If such an allergic reaction should indeed occur the importance of early diagnosis and treatment is obvious. The most satisfactory standard of diagnosis will entail recognition of the disease at a monosymptomatic stage.

This standard cannot be achieved, however, until disseminated sclerosis is made known to the general public. It is surprising how infrequently the patient communicates the first symptom to a doctor. Unless the lay public are taught to appreciate the potential significance of such symptoms as temporary weakness in a limb, transient dimness of vision, and diplopia the latter part of Buzzard's (1897) criticism, "the full-grown disease is frequently not recognized, the infant disease practically never," must remain justified.

Early diagnosis depends on proper appreciation of the disease process. We would like to stress the concept that in its early stages disseminated sclerosis is a functional nervous disorder. It was emphasized by Head (1920) that "all disease of the nervous system manifests itself