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Common Cold Symptomatology and Vitamin C

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Summary. The occurrence and severity of nine symptoms of the common cold were recorded daily for 35 weeks by girls and boys in four Dublin boarding schools. Half the children in each school received placebo or 200 mg tablets, or 200 mg or 500 mg tablets, of Vitamin C daily on a double blind basis. Diets or environmental conditions did not differ between the schools. A score for the severity of each symptom was obtained daily for all the subjects throughout the trial in the different treatment groups. The degree of association between pairs of symptoms was calculated. The symptoms of the common cold syndrome (the W-complex) tended to exist in two groups defined as Toxic and Catarrhal complexes (T- and C-complexes). The intensity and quality of W-complex symptoms were assessed in terms of the correlation value above which the constituent T- and C-complexes became manifest, the average correlation values of the constituent complexes, and the linkage of the symptoms in these complexes. The values for, and quality of, the complexes were dependent on the sex of the samples and the dose of Vitamin C administered. Boys tended to have more complicated W-complexes which broke down into T- and C-complexes with the lower dose of Vitamin C. These became more complicated when increasing doses of Vitamin C were administered. Girls had less complicated W-complexes, but more complicated T- and C-complexes, than boys. Increasing doses of Vitamin C made the girls' T- and C-complexes less complicated. Administration of Vitamin C appeared to benefit the common cold syndrome more in girls than in boys.

Evaluation of any therapeutic effect of Vitamin C on the common cold is often determined on purely subjective and clinical grounds [1]. The investigation carried out by Tyrrell and his colleagues [2], in which the effect of exogenous Vitamin C was observed on the number and duration of colds produced in volunteers by nasal instillation of viruses provided the major exception to this statement. This investigation may successfully have demonstrated the relationship between the common cold viruses and development of the common cold, but by modern standards of clinical trial methodology it could not be classified as a well conducted trial on the relationship between the clinical features of the common cold and the administration of supplementary Vitamin C [3]. The common cold is not a precisely defined disease [4]. Hope-Simpson [5] defined eight symptoms of "a cold". Preliminary observation in Dublin in 1965 suggested that these symptoms could be modified so as to provide a list more representative of the clinical features of the common cold. To both professional and lay men the term "a cold" has a clearly understood meaning: it signifies a short mild illness in which the main local symptoms are found in the upper respiratory tract, and in which nasal symptoms predominate [4].

The evidence presented by Pauling [6], about the effect of Vitamin C on the common cold indicates that ascorbic acid could be involved in the production of tissue resistance. No previous reports have been concerned with this possibility except that presented by Wilson and Loh [7]. These authors showed that leucocyte ascorbic acid concentrations are raised in subjects receiving exogenous ascorbic acid and at the same time a significant improvement occurs in cold symptomatology. Age, sex, and the degree of ascorbic acid saturation all have significant effects on ascorbic acid metabolism in the tissues [8]. Any investigation of the effect of exogenous Vitamin C on the course of the common cold should take into account such variations in the metabolism of ascorbic acid. A clinical trial using placebo tablets, and different doses of the vitamin on a double blind basis, must be used to investigate the effect of Vitamin C on the common cold. The clinical features of a cold can be assessed in terms of symptom severity and duration, and also of symptom association. The object of this paper is to describe the association between symptoms and to demonstrate how symptom association can be used as a basis for the study of the common cold.

Design of the Investigation

The occurrence and severity of symptoms of the common cold were recorded daily from the second week of September, 1967, until the end of May, 1968, by girls and boys in four Dublin boarding schools. During the first week of September the purpose of

the investigation was described to the children. They were told that they would be required to indicate daily whether or not they had any of the cold symptoms in the list on the form (Fig. 1). They were required to indicate when a symptom was not present. If a symptom was present, each individual was required to assess its severity subjectively, on a severity scale 1 to 4, and to record its daily severity on the form according to the instructions. They were also told that they would be required to take one tablet daily. The children who took part in the investigations were volunteers with the permission of their parents and school doctors. The teaching staffs of the schools co-operated fully in the investigations and arranged that the children filled in their forms, and took their tablets daily at specified times under supervision in each school [9]. Each child was issued with a bottle containing fifteen identical white tablets, and a new form, at two-week intervals, throughout the investigation by the school matrons. During school holidays, sufficient bottles and forms were issued to fulfil their requirements, and parents were asked to co-operate in ensuring that the children completed the forms and took the tablets.

Name .....

School .....

SEVERITY SCALE
Symptoms 1–9

0 = No Symptoms
1 = Extremely Mild
2 = Mild
3 = Moderate
4 = Severe

No. on Bottle

Date of Birth

Note: Please put a cross in the lower line against days of menstruation.

FORTNIGHTS – Please put ring round appropriate fortnight.

PLEASE CHANGE CARD ON 1st day of each fortnight.

1	2	3	4	5	6	7	8	9	10
6 Sept. *to* 19 Sept.	20 Sept. *to* 3 Oct.	4 Oct. *to* 17 Oct.	18 Oct. *to* 31 Oct.	1 Nov. *to* 14 Nov.	15 Nov. *to* 28 Nov.	29 Nov. *to* 12 Dec.	13 Dec. *to* 26 Dec.	27 Dec. *to* 9 Jan.	10 Jan. *to* 23 Jan.
11	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	
24 Jan. *to* 6 Feb.	7 Feb. *to* 20 Feb.	21 Feb. *to* 5 Mar.	6 Mar. *to* 19 Mar.	20 Mar. *to* 2 Apr	3 Apr. *to* 16 Apr.	17 Apr. *to* 30 Apr.	1 May *to* 14 May	15 May *to* 28 May	

	WEEK 1							WEEK 2						
Date														
1. Sore throat														
2. Cold in Head														
3. Cough														
4. Headache														
5. Ache in back or limbs														
6. Feverish														
7. Nasal Obstn.														
8. Nasal Disch.														
9. Out of Sorts														
Menstruation														

Fig. 1. Form for recording symptoms of the common cold as issued to MG girls.

The children consisted entirely of males or females in each school. The children in each school were randomly divided into two groups during the first week of September. The two groups in each pair of schools received different treatment on a double blind basis (Table 1). Codes were allocated to treatment groups using random number tables, the children in each school being given their num-

bers and medication on a class basis during the first day of the trial. The school forms and bottles were identified by colour codes and by individual school markings. Each child was issued with a number which was entered onto his form and bottle every fortnight. The number codes for identification of the medication were kept in sealed envelopes in the university. None of the envelopes was opened by the investigators during the course of the trial.

The contents of every bottle was checked on return and if it did not contain one tablet the child was withdrawn from the investigation unless an adequate explanation was received. Random chemical checks were carried out by an independent observer to ensure that the tablets remaining in the bottles were of the correct chemical constitution. Individuals were withdrawn during the course of the trial because forms were incorrectly completed, or because faulty tablet taking was detected, or for reasons related to school attendance or record. If an individual ceased to return his form for a period of two weeks for reasons related to the school, he was withdrawn from the trial. If he subsequently recommenced completing the forms, he was re-introduced into the trial as a new individual. In consequence the number of individuals receiving medication was slightly greater than the actual number of children in the schools as shown in Table 1. The school diets did not change during the course of the trial and did not differ ostensibly between the schools. The children were requested not to take any supplementary vitamins, and parents, school doctors and matrons ensured that this request was respected. The age-range of the children varied from 12—18 years. There was no evidence to indicate that the diets of the children or environmental conditions differed between the schools.

Table 1. *Composition and treatment of the school-groups receiving white placebo or Vitamin C tablets of identical taste and appearance on a daily basis*

School	Sex	Medication of Groups		No. of children	
		Tablet A	Tablet B	Tablet A	Tablet B
MG	F	Placebo	Vit C 200 mg	43	51
MB	M	Placebo	Vit C 200 mg	69	67
CG	F	Vit C 200 mg	Vit C 500 mg	47	40
MO	M	Vit C 200 mg	Vit C 500 mg	52	52

Results

Product moment correlation coefficients for the daily scores of the severity values of each symptom for the duration of the trial for all the subjects in each group have been calculated. These have been expressed as percentages for the boys and girls receiving placebo and 200 mg, and 200 and 500 mg, tablets of Vitamin C. The values for MB boys and MG girls while receiving placebo tablets are shown in Tables 2 and 3. These correlations are a measure of the extent to which symptom pairs tend to be reported together and extend over a range of 0 to 100%. The correlations are based on 7500—14000 observations in each of the eight treatment groups. Since the observations for each subject on successive days are obviously correlated, it would not be easy to attach a standard error to the calculated values. It may be of the order of 3 units in the figures presented. All symptoms are reported together to a varying degree, as demonstrated by the fact that there were no negative correlations in any of the groups. Tables 2 and 3 show that higher correlations tended to occur within two groups of symptoms, namely, symptoms 1, 4, 6 and 9, the Toxic complex, and symptoms 2, 3, 7 and 8, the Catarrhal complex. Symptom 5, ache in back and limbs, was not, in general, strongly associated with any of the other symptoms, although occasionally it could be associated with symptoms 4 and 9. These correlations are illustrated graphically in the diagrams accompanying each table. The diagrams show the symptom pairs which are correlated at values greater than the maximum value of the correlation between the two complexes. The maximum linking correlation (the W-complex value) between the groups in Table 2 is 40 (Symptom pair 2 and 9). The diagrams show that symptoms 4, 6 and 9, and symptoms 2, 3 and 8, are linked at correlations greater than 40, and that one symptom is completely dissociated in each complex. In the corresponding table and diagrams for the girls the W-complex value is 32. There is complete association between symptoms 1, 4, 6 and 9; only symptoms 3 and 7 are dissociated in the other complex. On the basis of symptom dissociations, whereby correlations within the two distinct complexes are higher than those between the complexes, the symptoms making up the common cold have been defined as the Toxic symptom com-

Table 2. *Correlation coefficients between symptom pairs during the common cold in MB boys*

	Symptom numbers	Toxic symptoms 1	4	6	9	5	Catarrhal symptoms 2	3	7	8
	1									
	4	34								
Toxic	6	40	44							
complex	9	30	40	43						
	5	22	38	34	30					
	2	36	31	39	40	21				
	3	35	24	32	29	16	49			
Catarrhal	7	16	19	15	26	13	39	29		
	8	28	23	32	33	16	49	43	33	
		1	4	6	9	5	2	3	7	8
W-complex		Toxic					Catarrhal complex			

Percentage values for correlation coefficients between symptom pairs in MB boys receiving placebo tablets. The value for the highest correlation coefficient linking Toxic and Catarrhal complexes (the W-complex value) is 40 (Symptoms 2 and 9). The paired symptom associations occurring at correlation values of more than 40 are shown in the diagrams below. Unassociated symptoms are circled.

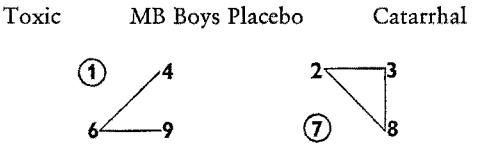
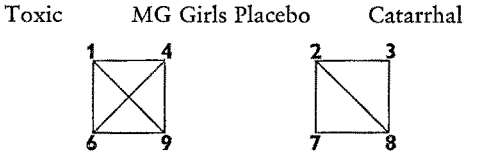


Table 3. *Correlation coefficients between symptom pairs during the common cold in MG girls*

	Symptom numbers	Toxic symptoms 1	4	6	9	5	Catarrhal symptoms 2	3	7	8
	1									
	4	34								
Toxic	6	35	35							
Complex	9	42	42	53						
	5	16	21	19	25					
	2	31	19	22	22	9				
Catarrhal	3	32	18	27	25	9	50			
Complex	7	13	9	9	14	2	46	23		
	8	26	21	16	27	10	68	48	55	
		1	4	6	9	5	2	3	7	8
W-complex		Toxic					Catarrhal complex			

Percentage values for correlation coefficients between symptom pairs in MG girls receiving placebo tablets. The value for the highest correlation coefficient linking Toxic and Catarrhal complexes (the W-complex value) is 32 (Symptoms 1 and 3). The paired symptom associations occurring at correlation values of more than 32 are shown in the diagrams below.

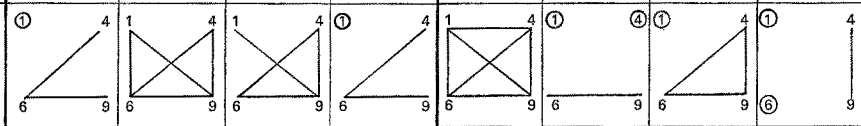
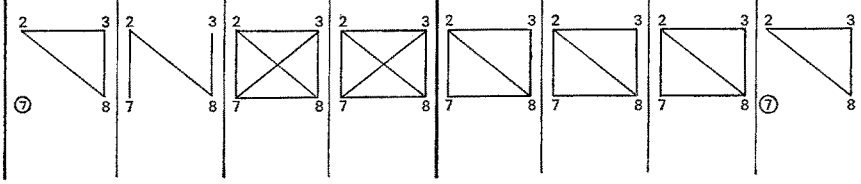


plex (T-complex), comprising: sore throat (Symptom 1), headache [4], feverish [6], and out of sorts [9], and the Catarrhal symptom complex (C-complex) comprising: cold in head [2], cough [3], nasal obstruction [7], and nasal discharge [8]. The higher maximum correlation (W-complex) value for the boys means that their symptoms do not break down into individual T- and C-complexes as readily as in the girls. The more numerous links in the diagrams, creasing doses of Vitamin C. The maximum values of the correlations in the W-complex are shown in the top row of Table 5. The T- and C-complexes are differentiated at higher correlation values, and are illustrated in the diagrams accompanying the table. Administration of 200 mg Vitamin C resulted in reductions in the maximum value for the W-complex in the boys. When 500 mg was administered to the girls the maximum value for the W-complex was

Table 4. *Average correlation coefficients (× 100) for individual cold complexes in the different treatment groups of boys and girls*

	Boys				Girls			
Cold complex	MB Placebo	MB Vit C 200 mg	MO Vit C 200 mg	MO Vit C 500 mg	MG Placebo	MG Vit C 200 mg	CG Vit C 200 mg	CG Vit C 500 mg
T-complex	38.5	31.2	30.2	22.7	40.2	35.3	29.7	22.2
C-complex	40.3	31.5	46.0	41.3	48.3	41.8	48.5	38.2
W-complex	28.6	21.4	19.1	18.4	20.7	19.4	22.1	17.3

Table 5. *Maximum correlation values in W-complexes, and differentiation of T- and C-cold complexes, in boys and in girls during treatment with Vitamin C*

	Treatment procedure							
	Boys				Girls			
	MB Placebo	MB Vit. C 200 mg	MO Vit. C 200 mg	MO Vit. C 500 mg	MG Placebo	MG Vit.C 200 mg	CG Vit.C 200 mg	CG Vit.C 500 mg
Maximum Correlation Values in W-Complexes	**40**	**28**	**26**	**25**	**32**	**37**	**35**	**27**
Symptom-pair associations in T-Complexes								
Symptom-pair associations in C-Complexes								

and the lower W-complex value, for girls, indicate that they tend to get more complicated Toxic or Catarrhal complexes than boys.

The average values of the correlations within the T-complex, within the C-complex, and for the correlations between Toxic and Catarrhal symptoms which together make up a whole cold (W-complex), are shown for all the experimental groups in Table 4. This table shows that the average correlation within each of the complexes diminished with in- also reduced. It can be seen from the diagrams in Table 5 that administration of Vitamin C reduced the number of linking associations in the T-complexes in girls. However, only the administration of 500 mg reduced the complexity of the C-complexes in girls. The administration of 500 mg Vitamin C reduced the number of T-complex associations in boys compared with the effect of 200 mg. 500 mg appeared to make the C-complexes more complicated.

Discussion

Occurrence of the common cold is shown by the appearance of a variety of symptoms. Constitutional upset may be its first indication. This may be shown by headache (Symptom 4), muscular aching (Symptom 5), lassitude and malaise (Symptom 9). When fever (Symptom 6) occurs it usually does so shortly after the onset [4]. The physical signs in the nose of obstruction (Symptom 7) or discharge (Symptom 8) were present in over half the infections [10]. A typical case at the height of the illness was characterised by nasal discharge and obstruction, sneezing and coughing (Symptoms 2 and 3), slightly sore throat (Symptom 1), headache, and malaise; nasal discharge was the most persistent symptom [11]. It is clear that associations tend to occur between the individual symptoms of the common cold. The degree and extent of these associations have been little investigated although cold symptoms have been divided into groups resembling those of T- and C-complexes [12].

Analysis of the association between symptom-pairs in the present investigation has demonstrated that the symptomatology of the common cold can be assessed in terms of symptom complexes. Symptom complexes are measured in terms of the maximum value at which the Whole syndrome of the common cold, the W-complex, breaks down into its constituent Toxic and Catarrhal complexes (T- and C-complexes). Symptom complexes can also be evaluated in terms of the average values for the correlation coefficients which make up the individual complexes in relation to the characteristics of the groups being investigated, sexes and schools in this case, and in relation to treatment being administered for control of the disease syndrome, placebo tablets and increasing doses of Vitamin C in the present investigation. Finally, symptom complexes can be analysed qualitatively by diagrams which illustrate how the individual complexes are made up of symptom pair associations which may be inter-linked to varying degrees. This method of analysis of symptoms, which together make up a disease syndrome, appears to be more sensitive than, and results obtained from it may be independent of, severity or duration of the syndrome in its entirety. The method is also capable of detecting alterations in the syndrome arising from prophylactic and therapeutic procedures.

The complexes differed between boys and girls who were receiving placebo tablets. The maximum value for the W-complex was lower in girls indicating that boys develop more complicated whole colds, and that girls tend to develop T- or C-complexes more readily and with less general pathophysiological disturbance than boys. Lidwell and Sommerville [13] have also reported that females had a higher incidence of colds than males in a rural community, the ratio being 1.4/1. Brimblecombe *et al.* [14] observed that the attack rate was higher in females over the age-range 20—39 years. The cold incidence has been shown to be 10—15% higher in female than in male office workers, and the relative frequency of Catarrhal symptom complexes was also greater in the females [12]. Wilson, Loh and Foster [15] have also demonstrated that the incidence, duration and severity of the cold complexes in the Dublin school children tended to be higher in females than in males during placebo therapy.

The administration of prophylactic Vitamin C altered the intensity and quality of the complexes differently in the two sexes. In boys, administration of 200 mg Vitamin C caused the W-complex to break down more readily into constituent C- and T-complexes. This effect appeared to occur in girls only when 500 mg of Vitamin C was administered. Administration of Vitamin C caused a general and progressive reduction in the average correlation values for all the complexes in both sexes. In boys the lower dose of Vitamin C appeared to increase the Toxic symptom associations, and the Catarrhal symptom associations were maximal when the higher dose was administered to the boys. Vitamin C in the lower dose had little effect on the girls' Whole cold syndrome which is in any case less severe than in boys. In contrast to the boys, the lower dose of the vitamin reduced Toxic symptom association, and the higher dose reduced Catarrhal symptom association in girls. It can be concluded that administration of Vitamin C had a more benefical effect at equivalent doses on the quality and intensity of constituent cold complexes in girls than in boys.

There appears to be a general disturbance of cellular metabolism at the time when Toxic symptoms are predominantly being appreciated. Clinically it is difficult to associate localised inflammatory changes in the respiratory tract with the presence of these Toxic symptoms [4]. The separate occurrence of the Catarrhal symptom complex indicated that it is characteristically associated with localized inflammation in the respiratory mucous membranes. Such inflammatory reaction is a frequent host response to respiratory viral illness and is not specific for a particular virus [16]. Toxic and Catarrhal complexes may be dissociated, and can develop and disappear independently of each other during the administra-

tion of Vitamin C. This suggests that the general disturbance of cellular metabolism, and the localized mucosal inflammation, are independent patho-physiological processes. The inhibitory action of Vitamin C on the development of the common cold was evident in both sexes, but its effect on overall cold symptomatology was dose and sex dependent. This observation suggests that development of symptoms of the common cold is determined to a significant degree by the ascorbic acid saturation of the host's tissues [8, 17]. The differences between symptom associations in the two sexes may be related to differences between the sexes in their ascorbic acid metabolism. Such differences in ascorbic acid metabolism occur between men and women at different ages during haemopoiesis [18]. Administration of supplementary Vitamin C to old men and women in the presence or absence of supplementary iron also demonstrates the ability of human females to make adjustments in their ascorbic acid metabolism during times of metabolic stress [19, 20]. Further evidence of this characteristic of females to compensate for deficiency of ascorbic acid has been demonstrated in female guinea-pigs which have the ability to make an adjustment in the metabolism of ascorbic acid during times of stress [20].

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