SULPHONAMIDES AND ACUTE TONSILLITIS

A CONTROLLED EXPERIMENT IN A ROYAL AIR FORCE COMMUNITY

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Anderson (1949), discussing the treatment of the acute throat, said: "The administration of sulphonamides has been intentionally omitted from the treatment of the acute throat. The efficacy of these drugs has never been convincingly demonstrated in such conditions. Since they are undoubtedly toxic materials, carrying appreciable risks of sensitization, their administration is inadvisable, and in certain conditions may even be dangerous." This opinion evoked considerable controversy, which was reflected in the correspondence columns of the *British Medical Journal* for some months.

From two points of view it is important that this controversy be soon resolved. The medical practitioner, faced with the problem of treating an acute throat, wishes to have available an effective remedy, and preferably one that does not require a complete bacteriological diagnosis before its administration, as this is uneconomical in time and money. From the national point of view, too, it is desirable that large sums of money should not be spent on drugs which may be neither effective nor safe.

It happened that we were in a position to carry out a controlled investigation with more ease than is common, as we were responsible for the medical care of a Service community of about 4,000 men. About 1,500 of these were aircraft apprentices under training.

As soon as it was decided to carry out an investigation Dr. T. Anderson was visited. It was found that he, too, was contemplating a controlled investigation. His cases were to be drawn from a suburban mixed population of Glasgow, whereas ours, from the R.A.F., were male and predominantly young. Treatment of the Glasgow cases would be in the home, whereas our treatment would be confined to those admitted to sick quarters. The age distribution of the Glasgow cases was likely to be wider, and both sexes would be included. In the R.A.F. cases, observation would probably be easier and a regimen of treatment certainly easier to enforce. From this it can be seen that the natures of the communities concerned in the two experiments were very different, and it was believed that the results, if the same, would thereby be strengthened. Dr. Anderson had already prepared record cards and formulated criteria for signs and symptoms. These were adopted for our experiment.

General Method

The general idea of the R.A.F. experiment was that one of us (T.C.M.) would organize the experiment and ensure that half the patients received "sulphatriad" and the others lactose tablets. (Sulphatriad was chosen

as it was a recent and elegant preparation, which is believed to have little risk of renal complications.) No one except T. C. M. would know whether sulphatriad or lactose tablets were being given to the patient. The other (I. H. W.) would be responsible for the medical care of the patients and for the clinical assessments and symptom-recording.

Before the experiment started, T. C. M. prepared a series of numbered envelopes containing slips marked Z or Y, which were placed in the envelopes in accordance with a random list prepared by Professor Bradford Hill. The sulphatriad and lactose control tablets, which were specially made by May and Baker Ltd. for the experiment, were put in plain bottles also marked with Z or Y. The bottles were changed four times during the experiment, thus:

Cases									
1-15	..	..	..	..	..	..	Z ₁	Y ₁	
16-30	..	..	..	..	..	..	Z ₂	Y ₂	
31-50	..	..	..	..	..	..	Z ₃	Y ₃	
51-75	..	..	..	..	..	..	Z ₄	Y ₄	
76-82	..	..	..	..	..	..	Z ₅	Y ₅	

The bottles containing sulphatriad were Z₁, Z₃, Y₃, Z₄, and Y₄. The doctor in medical care (I. H. W.) was unaware of these changes.

Procedure.—When one of the medical staff on the station made a diagnosis of acute tonsillitis, a second medical officer was called in and agreement was reached on the degree of severity—mild, moderate, or severe. This was a purely clinical judgment and took into consideration both local and general conditions. When the degree of severity and the necessity for admission to sick quarters for adequate treatment were agreed, the airman's name was placed on a nominal roll. His serial number on this roll was then used to draw a correspondingly numbered envelope, which in turn disclosed if he was Z or Y. The treatment described below was then instituted with Z or Y tablets accordingly. Before treatment started the first nose and throat swabs were taken.

Treatment

This was simple in the extreme. Except for visits to the lavatory the patient was kept strictly in bed until specific treatment was complete. Fifty tablets of either sulphatriad, 0.5 g., or lactose were given. Both types of tablet were identical in appearance. These were taken at four-hourly intervals, except between 10 p.m. and 6 a.m., as follows: 6, 4, 4, 3, 3, 2, 2, 2, . . . until the total of 50 was reached. Potassium citrate, 30 gr. (2 g.), was given four-hourly, and fluids were administered liberally during the time that tablets were being taken.

Other treatment was kept to a minimum, but no embargo was made—that is, no unethical withholding of treatment was permitted in order to make a more clean-cut experiment. In fact, other treatment was seldom necessary. Penicillin was prescribed on only two occasions. In one, it was given on the eighth day owing to a relapse, and the throat and general symptoms then cleared up in two days. In the second, acute otitis media developed on the ninth day and cure was effected in four days. Both these cases had been treated with the control tablets. One had beta-haemolytic streptococci in the throat and the other had not.

Other treatment given was as follows: (a) Treated cases: inhalations (menthol), one case; aspirin, one case. (b) Control cases: inhalations (menthol), four cases; mist. expect. stim. (N.F.), one case; aspirin, two cases.

Case Recording

This was done in two ways. First, selected symptoms and signs were recorded on a card of the type designed by Dr. Anderson. Symbols indicating the severity of the symptoms were also standardized. These were as follows:

Oedema: Present, +; moderate, ++; tonsils meeting uvula, and whole throat congested and oedematous, +++.

Exudate: S = spots on follicular exudate; P = patch of soft exudate; C = confluent, rather adherent exudate.

Adenitis (refers to tonsillar glands only): Present, +; easily palpated, almost obvious, ++; swelling noticeable, +++.

Tongue: c = coated; d = dry; n = clean; m = moist.

Drumheads: P = congested; Q = loss of light reflex; B = drumhead bulging; ot = otorrhoea.

Pain: +; ++; +++ (equals inability to swallow).

In addition the normal R.A.F. case sheet (F.41) was completed, giving more discursive information.

About 72 hours after treatment began the doctor in charge gave his clinical assessment of the progress of the case. He entered this as "good" or "poor."

Bacteriology and General Epidemiology

Swabs were taken from the nose and throat on diagnosis, at the end of treatment, and seven days after treatment was completed. These were examined at the R.A.F. Institute of Pathology, and reports on the organisms present were sent to us. For the purpose of this paper the results are given only as indicating the presence or absence of beta-haemolytic streptococci.

The collection of cases was undertaken from January 24 to June 15, 1950, when the experiment ceased owing to Service exigencies. At this time only 82 cases had been treated out of the 100 originally planned. There was no major epidemic, though two small beta-haemolytic streptococcal outbreaks occurred, each of about half a dozen cases. Each was localized to a single room in a barrack block. This does not necessarily incriminate the dormitory type of barrack room, as those cases occurred in apprentices who, if they slept in the same room, would automatically work together during the day; but the prima facie evidence is not to be set aside.

Results

The age grouping of the 82 cases is shown in Table I.

TABLE I.—Age Grouping

Age at Last Birthday	No.	Age at Last Birthday	No.
15	4	20	3
16	18	21	2
17	15	26	1
18	15	35	1
19	16		
		Total	82

Mean age = 17.88 years.

The medical officers considered 44 to be mild and 38 moderate or severe. Table II shows how these were distributed in relation to the presence of beta-haemolytic streptococci in the throat. Only the swabs taken on admission are considered here.

TABLE II.—Doctor's Initial Assessment of Severity Connected with Presence or Absence of Beta-haemolytic Streptococci in the Swabs taken at First Examination

Severity	Beta-haemolytic Streptococci		Total
	Present	Absent	
Mild	17 (47%)	19 (53%)	36 (100%)
Moderate or severe ..	25 (54%)	21 (46%)	46 (100%)
Total	42	40	82

No significant differences are shown here ($\chi^2 = 0.410$).

The results of treatment can be estimated in four ways: (1) by the daily record of signs and symptoms given on the cards; (2) by the appearance of complications; (3) by the subjective opinion of the medical officer recorded at about 72 hours; and (4) by the effect on the known pathogens in the throat—that is, the beta-haemolytic streptococcus: this is very indirect evidence, but may be admissible.

The second method is of no help here. There was only one complication in the 82 cases—an early acute otitis media. The youth of the subjects will be noted, and the fact that before their illness they were in fine physical condition. It is felt that this proportion of complications is not likely to be reproduced in the general population. Here, too, it may be said that there was no case with toxic effects due to the drug.

The daily recording of signs and symptoms in a standardized manner is, of course, the normal way of

TABLE III.—Number of Cases Returning to Normal, by Symptoms and by Day of Illness; with a Comparison Between the Means of the Figures Produced by Control and by Treated Cases

	Treated									Mean	Controls									Mean	Difference Between Means	Value of "t"
	No Symptoms Throughout	Day of Illness									No Symptoms Throughout	Day of Illness										
		1	2	3	4	5	6	7	8			1	2	3	4	5	6	7	8			
<i>Beta-haemolytic Streptococci Present</i>																						
Temperature*	3	—	3	12	5	2	—	—	1	3.0769	1	—	6	7	8	—	—	1	1	3.3333	+0.2564	0.1126
Oedema†	2	—	3	2	7	3	1	—	8	4.8077	1	—	6	4	5	1	—	1	6	4.3333	—0.4744	0.1366
Exudate‡	1	—	5	6	8	2	3	1	—	3.6538	—	—	4	5	4	5	2	2	2	4.4167	+0.7629	0.3484
Adenitis§	2	—	1	2	5	2	3	—	11	5.5385	2	—	2	3	3	2	—	12	5.8750	+0.3365	0.0636	
Pain	—	—	4	9	8	4	—	1	—	3.6154	—	—	1	6	6	6	4	—	1	4.4167	+0.8013	0.3140
<i>No Beta-haemolytic Streptococci Present</i>																						
Temperature*	4	—	2	8	—	—	—	1	2	2.3333	5	—	4	3	1	2	2	—	—	2.5294	+0.1961	0.1037
Oedema†	—	—	2	3	3	2	1	2	2	4.7333	2	—	3	1	4	2	—	5	—	4.4118	—0.3215	0.1069
Exudate‡	—	—	4	2	3	—	3	—	3	4.5333	5	—	2	4	1	4	—	—	1	2.8235	—1.7098	0.7221
Adenitis§	2	—	—	2	1	1	2	—	7	5.5333	1	—	1	3	2	3	—	7	—	5.8235	+0.2902	0.0578
Pain	—	—	1	9	3	2	—	—	—	3.4000	1	—	2	4	3	4	2	1	—	3.9412	+0.5412	0.2208

* The number of patients in whom the temperature returned to normal (98.4° F.—36.9° C.), both morning and evening on this day, for the first time. This last phrase is important, as many patients showed a transient rise of temperature on their first day out of bed.

† The number of cases which have shown a diminution of oedema for the first time on this day—that is, from +++ to ++, ++ to +, or + to nil.

‡ The number of cases showing no exudate on the tonsils or pharynx for the first time on this day.

§ The day on which adenitis is first seen to diminish.

|| The day when pain first disappeared.

estimating any kind of cure or recovery. The choice of those symptoms and signs which can most advantageously be used is not easy. Of the eight originally put on the card we have rejected three—pulse rate, tongue appearance, and ear-drum appearance; the first two because no apparent change occurs with recovery, the third because only one case in the series showed ear signs of any kind. Other signs and symptoms were considered and rejected. As an example, frontal headache, a common symptom, might be caused by the throat, by the treatment, by constipation, or by reading in bed in a bad light.

As has been said above, the cases were taken as they came and divided into "treated" and "control." No account was taken of bacteriological findings. However, it is felt that a more accurate idea of the results is obtained if they are divided according to the presence of the beta-haemolytic streptococcus. In these results (Table III), cases are called positive if the beta-haemolytic streptococcus is found on any swab during the experiment.

We believe that the presence of a raised temperature and of pain are the two most reliable of the signs and symptoms, the former because of its complete objectivity and the latter because it appeared to us to be a clear-cut fact about which the patient had no doubts. The presence of exudate follows a close third, whereas it is not possible to apply this same degree of objectivity to minor fluctuations in oedema and adenitis. In a considerable number of cases diminution of "oedema" and "adenitis" occurred for the first time on the eighth day. This is because we were forced to include in this column all those cases still unchanged at the end of a week or discharged from sick quarters still not completely normal. This does not apply to "temperature" and "pain," and their arithmetic means will therefore be more accurate than those of others.

The arithmetic means of the number of days taken by the cases to show cure or improvement as denoted by individual signs have been calculated. The differences between the means of the treated and those of the control cases are shown. The differences have been examined for significance by the "t" test. The values of "t" are also given. They do not reach significant levels.

There was no difference in the rate of recovery between control and treated cases whether the beta-haemolytic streptococcus was present or not.

It will be seen from Table IV that there is a marked difference between treated and controlled cases in rapidity of cure.

TABLE IV.—*Doctor's Assessment of Rapidity of Cure at About 72 Hours*

Cases	Good Cures	Poor Cures	Total
Treated	34	7	41
Control	19	22	41
Total	53	29	82

The χ^2 test gives the value of 10.46, which value is much greater than 3.84, the critical significance value for one degree of freedom. The relationship of "good" cures and treatment is therefore very unlikely to be due to chance.

A fourth piece of evidence is given in Table V. This shows that the administration of sulphatriad had no

TABLE V.—*Survival of Beta-haemolytic Streptococci in the Throats of Cases Treated with Sulphatriad and in Those of Control Cases*

	Treated	Control	Total
Appearing in first swab and remaining later	16	10	26
Appearing in first swab and disappearing on treatment	8	7	15
Total	24	17	41

effect on the survival of beta-haemolytic streptococci in the cases examined. The χ^2 test gives a value of 0.0341.

Comments

This experiment was begun with the very simple idea of attempting to find out whether sulphonamides were efficient and economically reasonable drugs to use in the treatment of acute throats, in particular under Service conditions. For convenience in control, the term "acute throat" was restricted to cases in which there was a frank inflammation of the tonsils. In one way the simple trial has produced a simple answer—that is, that there is no difference which shows in normal clinical recording between the recovery of patients suffering from this condition who are treated by rest in bed, copious fluids, and 25 g. of sulphatriad and patients who do not receive the drug.

However, it must be said that the doctor in clinical charge was able to detect which tablets were sulphatriad and which lactose by the better effect of the former on the appearance of the patient. It was also shown (Table IV) that the doctor's assessment of "good cure" at 72 hours was significantly associated with sulphatriad medication. It is felt that these two very subjective results cannot overrule the negative result shown in Table III, and from a severely practical point of view simpler and less potentially dangerous remedies must be recommended. (The absence of complications in the experiment is surely to be expected in the conditions under which it was conducted, but renal complications are not so easy to avoid in some climates in which R.A.F. medical officers have to practise.)

These subjective findings may be considered to explain the disagreements with Anderson's opinions mentioned at the beginning of this paper. They do not, in our opinion, justify the routine use of a potentially dangerous drug. Other methods can be found to improve well-being if the difference in speed of recovery is to be measured only in hours.

It is, of course, understood that a decision to advise against any general use of sulphonamide drugs in the treatment of acute throats must also depend on two other considerations—on the number of toxic reactions and on the value of these drugs in preventing epidemic spread. The present experiment gives no answer to these two aspects of the problem.

Summary

Eighty-two consecutive cases of acute tonsillitis were divided into two equal parts in a random manner. They were all treated by rest in bed and given copious fluids to drink. One half were given 50 0.5-mg. tablets of sulphatriad. The other half received an equal number of lactose tablets identical in appearance to the former.

Analysis of clinical records reveals no difference between controls and treated cases in the speed of recovery from various symptoms. The medical officer in clinical charge

was, however, able to make an estimate of "goodness of cure" which had a significant relationship to administration of sulphatriad.

It is felt that the routine administration of sulphonamides to patients with acute tonsillitis cannot be supported by the results of this experiment.

We wish to thank Professor Bradford Hill and Dr. D. D. Reid for their help and advice. We also are grateful to Messrs. May and Baker Ltd. for their kindness in providing both sulphatriad and control tablets for these experiments, and particular thanks are due to Mr. E. J. Baines, of the New Products Division. We are indebted to the Director-General of Medical Services, R.A.F., for permission to publish.

REFERENCE

Anderson, T. (1949). *British Medical Journal*, 2, 860.

"SORE THROAT" IN GENERAL PRACTICE

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Acute tonsillitis, especially as it occurs in general practice, has received little study in recent years from the point of view of either epidemiology or treatment. The Commission on Acute Respiratory Diseases (1944) made an intensive study of the problem in American troops during the recent war, but, valuable as this investigation undoubtedly is, its findings are applicable only to young healthy adults, and, indeed, to young adults living in artificial surroundings which would tend to encourage infectious "in-breeding." No excuse is needed, therefore, for presenting some information on the epidemiology of "sore throat" as it is seen in ordinary urban practice. But if there is a need to know what clinical material is comprised in this general descriptive title, there is an equal need to study what is the best method of treatment. Criticisms, based largely on clinical impressions, were made in the correspondence columns of the *British Medical Journal* following a statement that the sulphonamides had little value as a method of treatment in such conditions (Anderson, 1949). A study was therefore conducted to secure some factual information. The present paper is based upon the records of the first 100 cases.

Material and Methods

The patients studied were encountered in the general practice of three of us (R. B., D. McF., and W. B.); they consisted of all those who complained of "sore throat" as the leading symptom. It was arranged that throat swabs would be submitted from such patients, who would subsequently be visited by one of the epidemiological team, if possible within the following 24 hours. At this visit a second swab of the throat and a swab of the post-nasal space (taken through the nose) were

obtained. Two special cards were drawn out, one of which was to be used by the general practitioner so that uniform records of the duration of signs and symptoms could be kept; the other was used to record the main epidemiological data. The experiment was begun in January, 1950, and still continues.

Quantities of tablets were prepared by May and Baker Ltd. which, though differing in composition, were similar in appearance. One set contained 0.5 g. of sulphanilamide, another 0.5 g. of "sulphatriad," and a third 0.5 g. of lactose. Each lot of tablets was referred to by the letters A, B, or C, the proper constituents being known only to the hospital dispenser. The practitioners have stated that they were unaware which tablet was which, except on one occasion when a patient developed a sulphonamide rash, whereupon the lettering was changed.

During January and early February each doctor was supplied with a particular tablet which he was to use for those patients who came into the trial, the intention being that the doctors were to employ a different medicament each month. This method, which was chosen for its obvious simplicity, was open to criticism on epidemiological grounds, for it was possible that the type of tonsillitis seen in one month might be different from that seen in another. Accordingly, during the remainder of the period each practitioner carried a supply of all three tablets, and the method of treatment was thereafter dictated by the use of a set of random numbers which were written on the cards supplied to the practitioner.

During the preliminary period (January–February) the practitioner who had been given the lactose tablets saw the greatest number of sore throats. Accordingly when the whole series is summated there is some inequality in the treatment groups. Thus there were 26 cases in the sulphanilamide group, 26 in the sulphatriad group, and 43 in the lactose group. It is felt that, since the method of treatment was at no time selected by the doctor, no serious harm arises from analysing all of the patients in this preliminary report. In four cases the practitioner's card was lost, so that the method of treatment was not known, and in one case, in error, the allocated method of treatment was not adhered to. It is perhaps worth commenting that prior to the trial one practitioner was firmly convinced of the value of sulphonamides in such cases, the second used them with fair frequency, whereas the third seldom prescribed them.

The throat and post-nasal swabs were treated in the following way. A Löffler's slope, and blood-agar and gentian-violet blood-agar plates were inoculated, care being taken to ensure that the whole swab was rubbed on the surface of the plates. A direct film was also examined for the presence of Vincent's organisms. Cultures were examined at the end of 18–24 hours' incubation. Particular attention was paid to the presence of β -haemolytic streptococci (H.S.), and when these were present the following notation was used: + = up to 5 colonies; ++ = up to 50% of the growth; +++ = more than 50% of the growth. The predominance of any other organism was noted and an attempt made to type any pneumococci isolated. Under the conditions of the experiment it was not possible to carry out serological tests which might have had the value of defining more completely the streptococcal aetiology.

As the study has two aspects—namely, epidemiological and therapeutic—the results will be described under these subheadings.

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