Blood levels with sodium sulfapyridine varied between 10.5 and 25.0 mg in 100 cc of blood. In terms of milligrams per hundred cubic centimeters, at different intervals after injection, the blood levels on the twice daily schedule were at 3 hours 25.0, at 6 1/2 hours 15.0, at 7 1/2 hours 11.0 and at 12 hours approximately 10.5. With sulfapyridine in oil given at noon and midnight, the blood levels did not rise as high or drop as low as with the sodium salt. Three hours after injection the blood level varied between 7.0 and 15.6 mg per hundred cubic centimeters, at 5 1/2 hours it was 15.0 and at 11 hours 12.2.

Trials with other sulfonamides were not sufficiently extensive to permit of any definite conclusion. With sodium sulfadiazine we were able to cure nearly all mice of a small batch when treatment was commenced the fifth day. It is of particular interest that this result was obtained after only three days of treatment, the mice receiving 0.02 Gm. the fifth day in two equal doses twelve hours apart, 0.03 Gm. on the sixth in three equal doses at intervals of eight hours, and a single dose of 0.01 Gm. on the seventh day. While these results are encouraging, the amounts injected, although reported to be safe, were found to be dangerously near the toxic dose, blood levels rising to above 20 mg. per hundred cubic centimeters three hours after injection. It is possible that smaller safer doses might prove effective. Sulfathiazole in oil started on the tenth, twelfth, thirteenth or fourteenth days after infection cured no mice; the blood levels obtained, 8.75 mg. per hundred cubic centimeters at 7 hours and 10.4 at 12 hours, were perhaps too low for maximum benefit. As already noted, mice treated with sulfapyridine ten to fourteen days after infection were cured in about half the cases; however, the blood concentrations attained varied between 7.0 and 15.6 mg. per hundred cubic centimeters.

CHRONIC INFECTION OF CURED MICE

Recently one of us has shown 3 that mice receiving very small doses of virulent toxoplasmas will recover but remain carriers, the infection persisting as an inapparent one for long periods of time. When the carriers died or were killed and the viscera examined, the brain in every instance was found to be heavily infected with living virulent organisms. Other data were presented which indicate that the carrier state may exist in man.

The question naturally arose whether in the present experiments the sulfonamides in effecting a cure of the disease eradicated the infection or only aided in producing the carrier state. The evidence is unequivocal; we have no proved case of sterilization of the infection, for in every instance tested the cured mice were found to be carriers. The toxoplasmas were present in the brain, being usually quite numerous and shown in every test to be virulent by passage to new mice.

This result was obtained whatever the drugs used: sulfapyridine, sodium sulfapyridine, sodium sulfadiazine and sulfathiazole. It also seemed to be independent of the length of the period of administration as well as of the dose of drug and was found to occur even in experiments (not otherwise reported in this paper) in which the drug was given prophylactically before infecting the animals. It seems justified to conclude, therefore, that the sulfonamides cannot be relied on to eradicate the carrier state.

1. Sulfapyridine is strikingly successful in curing acute toxoplasmosis in mice.
2. The recovery rate is the higher the earlier in the course of the disease treatment is started. When treatment is initiated at the expiration of one-third the period of expected survival, nearly all animals recover. If treatment is delayed beyond the end of the second third of this period, only half the animals survive. However, some animals are cured by sulfapyridine administered as late as three days before expected death.
3. Therapy cures the disease but it does not sterilize the infection. The cured mice remain carriers and retain virulent organisms in the brain.
4. The results appear to warrant use of the sulfonamides in treating human acute toxoplasmosis.

SULFADIAZINE IN THE TREATMENT OF THE COMMON COLD

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The common cold derives its medical importance chiefly from the fact that it is followed so frequently by secondary infection. The uncomplicated cold, now generally accepted as caused by a filtrable virus, runs a mild course, usually afebrile, and clears up completely in four to seven days. On the other hand, a cold complicated by a secondary bacterial infection which may involve the sinuses, middle ear, mastoids, larynx or lungs can lead to a fatal outcome. It is evident, therefore, that the cold problem would be greatly simplified if all colds could be retained in the uncomplicated form by some relatively harmless medication. The value that sulfadiazine, the least toxic of the sulfonamides, might have in this role is the consideration of this study.

It is generally agreed that the sulfonamides have little or no effect on the virus initiating the common cold, but it has been accepted that they are effective agents against the pneumococcus and the hemolytic streptococcus. Also there is evidence that they are effective, but to a lower degree, against Haemophilus influenzae and the hemolytic staphylococcus, the other two most common secondary invaders of the respiratory tract following colds.

The literature on the use of the sulfonamides in acute coryza per se is comparatively meager, although its use in localized disease of the respiratory tract following colds is quite extensive. But even in such common conditions as tonsillitis and sinusitis there is no unanimity of opinion regarding the indications and value of the sulfonamides. In 1937 Long and Bliss 4 reported favorably on the use of sulfanilamide by mouth in acute pharyngitis and tonsillitis. On the other hand,

Rhoads and Afremov 2 in a controlled series of cases of pharyngitis and tonsillitis found that sulfanilamide did not lessen the severity of symptoms, reduce the incidence of complications or shorten the duration of the "cold" or the carrier state. Kernan 3 found that sulfanilamide orally did not alter the ordinary course of tonsillitis but that complications were fewer when it was used. This opinion is the one most commonly accepted today, even though there have been improvements in sulfanamide therapy through the introduction of drugs more effective and less toxic than sulfanilamide.

In sinusitis there is particularly great divergence of opinion on the value of the sulfonamides. Turnbull 4 reported that a large proportion of patients with chronic sinusitis were benefited by spraying the nasal cavities with a 5 per cent solution of sodium sulfathiazole. No untoward effects were observed in Turnbull's series of 47 cases. This enthusiasm for the local use of the sulfonamides in chronic sinus infection has not been borne out by later reports, and there have been studies indicating that a 5 per cent sodium sulfathiazole solution is deleterious to the mucous membranes. Gundrum 5 reported the effect of sulfanilamide preparations on the nasal mucous membrane of rabbits and found that sodium sulfathiazole in 4.7 per cent solution was locally destructive following nasal instillation. Sodium sulfadiazine, while not so frankly destructive, was also injurious. Otolaryngologists are in greater accord on the value of the sulfonamides in acute sinusitis and in acute otitis media. Bowers 6 believes that they exert their effect most strikingly in fulminating sinus infections and that in acute otitis media, if oral chemotherapy is instituted early, the duration of discharge and the number of mastoidectomies are both reduced by 50 per cent. For local use Bowers 6 prefers sulfadiazine or sulfathiazole powder applied directly to the mucous membranes. Silcox and Schenk 7 have used a 5 per cent suspension of microcrystalline sulfathiazole for the treatment of acute and chronic sinusitis, the suspension being instilled directly into the sinuses. In addition to the differences of opinion over the relative value and safety of the different sulfonamides in the treatment of acute and liquid forms, the relative value and safety of oral and local administration remains highly controversial.

The value of the routine use of the sulfonamides in the treatment of the common cold has been widely speculated on in medical circles, but very little detailed investigation has been carried out on this problem. Bordley, Crowe, Dolowitz and Pickrell 8 at Johns Hopkins Hospital treated a small alternate group of nurses coming down with colds by spraying the pharynx and nasal passages with a 2.5 per cent sulfadiazine in 8 per cent triethanolamine solution. In addition to definite symptomatic relief they observed a reduction in complications and a decrease in the secondary bacterial invaders in the nasopharynx, particularly the hemolytic streptococcus. While this study is very suggestive, it is not convincing because of the small number of cases included. Furthermore, the method of treatment reported is not entirely practical because in order to obtain results it is necessary to spray the pharynx eight times daily for the first two days and then five or six times for three days.

Rusk and van Ravenswaay 9 have recently published their results on the oral use of sulfadiazine in the treatment of acute febrile respiratory infections which were seen in a large army station hospital during the winter of 1942-1943. Doses of drug (3.0 Gm. initially followed by 1.0 Gm. every four hours) similar to those used in pneumonia were administered until improvement occurred. In the 317 treated patients compared with 314 comparable controls the authors observed no significant difference in either the length of the febrile period or in the period of hospitalization. Contrariwise, Siegel 10 observed decided differences with and without sulfadiazine in alternate groups of feebleminded children with acute febrile respiratory infections, to which such individuals are particularly susceptible. In this reported series the incidence of serious secondary infections and the duration of the febrile period were considerably lessened.

This brief summary of the literature indicates that the exact role of the sulfonamides in the treatment of upper respiratory infections has not been accurately determined. Our purpose in this study has been (1) to determine the effects of small oral doses of sulfadiazine on the nasopharyngeal flora of persons suffering from acute coryza and (2) to ascertain, if possible, the indications for the use of sulfonamide therapy in upper respiratory tract infection, estimating the benefits to be expected in such cases from this therapy.

METHOD

The subjects were volunteers from the personnel of the New York Hospital. 11 They attended a "cold clinic" where they could be studied and treated systematically. To the majority of them colds had become a serious problem because of their frequency and severity.

At the beginning of observation a detailed respiratory history was taken and a careful examination 12 of the upper respiratory tract was made. At the start of therapy and every second or third day during the follow-up, the following procedures were carried out:

1. Oral temperature.
2. Complete blood count on all those actually receiving sulfadiazine, and hemoglobin determination on the others.
3. Record of symptoms with their intensity at time of visit.
4. Examination of the upper respiratory tract.
5. Nasopharyngeal culture.

In addition, gross and microscopic urinary examinations were made at the start, and later examinations were made if there was indication for them. Also the levels of sulfadiazine in the blood were determined twice during the course of therapy by a micromodification of the
Bratton and Marshall method. This procedure served as an excellent check as to whether the subject was taking the drug as directed.

The treatment as far as the patients knew was the same in all cases. In addition to written directions for the usual symptomatic and hygienic measures they all received an envelope containing 24 tablets with instructions to take 2 immediately and then 2 three times daily (on rising, at midday and at bedtime) until the medicine was gone. At the start of the study all of the subjects received sulfadiazine, which meant that they received 1.0 Gm. three times daily for four days, or a total amount of 12 Gm. During the latter part of the study alternate patients received a placebo tablet which could not be distinguished from the drug. The treatment usually was commenced on about the second or third day of the cold when symptoms were established, but a few late cases also were included. The period of time covered by this study extended from October 1941 to June 1942.

Nasopharyngeal cultures were taken at the time therapy was initiated and at frequent intervals (usually every second day) thereafter in order to determine the changes that occurred in the nasopharyngeal flora following the therapy.

**CULTURE TECHNIC**

A small cotton swab on a curved malleable aluminum wire was inserted into the posterior nasopharynx. West tubes were not used, as it is possible with skill to avoid contamination of the swab with the saliva. The swab was put in a tube of 3 cc. of hormone blood broth. With as little delay as possible a measured amount of this infected broth was spread directly on blood hormone agar plates. The blood broth after incubation for four hours, was also injected intraperitoneally into white mice as a further check on prevalence of the pneumococcus types and other pathogens. The blood agar plates were incubated for forty-eight hours and read. An attempt was made to estimate the number as well as the type of the various pathogenic agents that were encountered. For example, if Haemophilus influenzae (Pfeiffer's bacillus) was encountered the approximate number and relative proportion of these organisms on the plate were determined. The total count and the prevalence of individual pathogens were compared with the findings in each subsequent culture. Serial cultures made it possible to determine any change in either quantity or quality of the organisms found in the nasopharyngeal cultures.

**INITIAL CONTROL STUDY**

Before initiating the therapy of persons with colds, we gave the drug to a group of 6 normal subjects. Nasopharyngeal cultures were obtained daily to determine the effect of sulfadiazine on normal nasopharyngeal flora. This work was done in August, when pathogens such as pneumococci and beta hemolytic streptococci are normally at a low level in the throat. The striking features of this initial study were:

1. The uniformity of character and relative distribution of various nasopharyngeal organisms in the throat of any given individual.

2. The pronounced reduction of normal nasopharyngeal flora that followed administration of sulfadiazine. When the blood level reached a concentration of 4 to 6 mg. per hundred cubic centimeters the effect of the drug was clearcut.

3. The rapid return of flora to former prevalence and relative distribution within two or three days after the drug was discontinued.

The results of a typical experiment are summarized in figures 1 and 2. In the first illustration photomicrographs of daily blood agar plates from 1 subject show the decrease in the normal nasopharyngeal flora following the administration of sulfadiazine 1 Gm. three times daily for four days. Figure 2 shows the total colony count and correlates it with the dosage and blood levels of sulfadiazine. These illustrations show a striking change during the period of treatment but rapid return of the organisms to their normal pattern after the cessation of drug treatment.

**ALTERNATE CASE STUDY**

Seventy-two separate colds in 66 persons were treated in the "cold clinic" and carried through a complete series of bacteriologic and clinical observations. In the 72 cases the 3.0 Gm. daily dosage of sulfadiazine was administered to 48 subjects and acceptable blood
sulfonamide readings were made. Nineteen received the control tablets and 5 were given sulfadiazine tablets but the blood level determinations indicated either that the drug was not taken or that it was not absorbed. Therefore, at the start, the cases can be divided into two groups; 48 in which sulfadiazine was administered and 24 in which specific therapy was not administered.

Before analyzing the results in the cases in which sulfadiazine was administered it seemed wise to create a base line for comparison by studying the control series. This group included 24 patients: 19 assigned originally to the control group and 5 from the treated series who, it was evident, did not take or absorb the drug. The bacteriologic findings from the nasopharyngeal cultures in these cases followed a pattern already described by Smillie.14 Early in the cold and during the stage of the watery secretion from the upper respiratory tract the total bacterial count was reduced. However, after this the total count increased, frequently with a definite predominance of one or more of the pathogens such as the pneumococcus, beta hemolytic streptococcus or Haemophilus influenzae. Of the 24 cases, 4 showed a combination of pneumococcus (types 3, 8, 20 and 21) and H. influenzae, which during the height of the infection appeared on the plates in large numbers. In 8 cases the pneumococcus (types 6, 8, 11, 20 and 31) was isolated in the first examination. The pneumococcus grew out in increased numbers in all instances but 1, in which it disappeared. Haemophilus influenzae was present alone four times and in 2 cases showed increasing numbers on the subsequent cultures. The remaining 8 control cases showed only the usual throat organisms, but in all of these the growth increased during the period of the infection, after the transient decrease.

Clinically these 24 patients showed an ordinary run of colds. Several lost time from work, 1 because of a secondary tonsillitis and another because of severe bronchitis and sinusitis with fever. Six developed a moderate but short lasting sinusitis and 2 had a moderate bronchitis. The colds of 11 patients were uncomplicated except that 3 had prolonged sore throats. Three gave such vague descriptions of their symptoms that they could not be used in appraisal of the clinical findings.

A diagrammatic representation of the course of symptoms and changing nasopharyngeal flora in a control case is shown in figure 3. A key to symbols for symptoms and organisms adjoins this graph. In following symptoms, particular attention was given to malaise, sore throat, rhinorrhea, sinus congestion, hoarseness and cough, and each of these symptoms when present was graded as to whether it was slight, moderate or severe. The organisms that were most carefully identified and included in the graphs are pneumococcus, beta hemolytic streptococcus, H. influenzae and hemolytic Staphylococcus aureus. Staphylococcus albus, alpha and gamma streptococci and diphtheroids were almost universally present in the nasopharynx.

Figure 3 (M. H.) shows the onset with slight malaise, sore throat, rhinorrhea, hoarseness and cough. On the second day the sore throat and rhinorrhea became moderately severe, and on the fifth day the malaise also increased. These symptoms continued through the seventh day but had disappeared by the tenth day except for a slight rhinorrhea. The first culture was not made until the fifth day; consequently the initial decrease in organisms does not show. This culture showed a heavy growth of Staphylococcus albus and other mouth organisms and a few colonies of hemolytic Staphylococcus aureus and Haemophilus influenzae. On the seventh day, when the cold was still active, the culture continued to show a heavy growth with an increase in the number of colonies of Staphylococcus aureus and H. influenzae. On the tenth day, when the symptoms had subsided, the total number of organisms as well as the number of pathogens in the nasopharynx were decreasing.
TREATMENT WITH SULFADIAZINE

In the cases treated with sulfadiazine the most striking effect was the uniform reduction in the number and variety of organisms in the nasopharynx as measured by the serial nasopharyngeal cultures. Thirty-eight of the 48 cases studied showed a moderate or pronounced reduction in the total colony count. In some of these the effect was striking, showing on the plates a change from a heavy growth to a few scattered colonies. The total number of pathogens was also consistently reduced, but this seemed generally to be in proportion to the total reduction of organisms. Usually the pneumococcus, beta hemolytic streptococcus or other pathogen would not entirely disappear but would continue to show a few colonies and then return in larger numbers when the sulfadiazine was discontinued. The rapid return was pronounced in 6 of the 48 cases. In 10 instances no reduction in organisms was measured, but 5 of these showed a scant growth and no pathogens at the start, and the flora was held in check at that level.

The prevailing significant secondary organisms encountered in these cases were the pneumococcus in 20 patients, Haemophilus influenzae in 13, beta hemolytic streptococcus in 7 and hemolytic Staphylococcus aureus in 4. Nine persons in this entire group harbored no recognizable pathogens. In a number of instances more than one of these organisms were isolated. The pneumococcus types encountered were type 3 four times, type 6 three times, type 8 twice, type 18 three times, type 15 twice and types 4, 7, 11, 19, 20, 21 and 29 each once.

The clinical findings were not convincing. The average duration of the sulfadiazine treated cold was 8.1 days and that of the control 9.7 days. It can be appreciated that in a condition such as the common cold these figures are not significant. Of the 48 colds treated, 32 showed no recognizable secondary infection though they occurred in persons who usually suffered from complicated colds. Six persons developed sinusitis, bronchitis or both after the sulfadiazine treatment had been concluded. Five of the 6 had mild infections, but in 1 there was a moderately severe sinusitis and bronchitis (fig. 8), which lasted several days. Five patients had mild sinus and/or bronchial symptoms which developed during sulfonamide therapy. Five patients had irregular courses which could not be satisfactorily appraised. The patients were asked for their own opinions, and 34 expressed satisfaction with the therapy. Nine stated that they noticed no difference from previous colds, 1 was worse and 4 had no opinion to offer. These personal opinions were interesting, but we know how misleading such information can be. Figures 5, 6, 7 and 8 show the course of symptoms and changes in nasopharyngeal flora following sulfadiazine 1 Gm. three times daily for four days. The cases that are included represent the various types of response observed in the study. In the first case (fig. 5, G. F.) the onset was with a slight soreness of the throat, malaise and moderate rhinorrhea and sinus congestion. On the fourth day of the cold, when sulfadiazine therapy was started, in addition to the symptoms of onset there was also a moderate cough, and the nasopharyngeal culture showed a heavy growth which was almost pure hemolytic staphylococcus aureus. Two days later (sixth day) the cold was much improved clinically but the nasopharyngeal culture still showed many colonies of hemolytic Staphylococcus aureus even though the blood sulfadiazine was 9.5 mg. per hundred cubic centimeters. Following this the symptoms disappeared almost completely; the nasopharyngeal culture showed a decided reduction in total organisms and almost complete disappearance of the hemolytic Staphylococcus aureus. This is the type of response that occurred in most of our cases.

Figure 6 (J. L.) shows a case that was not studied and treated until the tenth day of illness, when a very severe malaise, sore throat, rhinorrhea, sinus congestion and a moderate cough were present. The culture showed a heavy growth with many colonies of H. influenzae and a few colonies of hemolytic Staphylococcus aureus. The cold had progressed to the stage of secondary infection. Following the institution of sulfadiazine therapy the symptoms subsided and the nasopharyngeal culture cleared rapidly.

Figure 7 (B. P.) again shows the course in a person treated by sulfadiazine 1.0 Gm. three times daily for four days. The onset this time was a slight sore throat

KEY

SYMPTOMS
Melaise
Sore Throat
Rhinorhea
Sinus
Hoarseness
Cough

FLORA
Pneumococcus
B. Hemolytic Streps.
H. Influenzae
Hem. Steph. Aureus
Steph. Albus
Other

Fig. 4.—Key of symbols for symptoms and nasopharyngeal flora.

Fig. 5 (G. F.).—This patient shows a favorable clinical and bacteriologic response to sulfadiazine treatment.
followed by severe rhinorrhea, moderate malaise and sinus symptoms. Treatment was instituted on the first day. The symptoms remained about the same for three days and then subsided slowly, disappearing except for a slight rhinorrhea on the seventh day. The nasopharyngeal culture at the time therapy was instituted showed a few pneumococci and a very few colonies of H. influenzae; these disappeared after treatment was started and the total number of organisms was considerably decreased. When treatment was discontinued the number of organisms increased and a few pneumococci were again found, although there was no return of symptoms. This person ordinarily has a long course of sinusitis following a cold (two to four weeks).

Figure 8 (S. M.) is the graph of a case of acute coryza which started with an irritated throat followed by malaise, rhinorrhea and sinus congestion. Treatment was started on the second day, when the rhinorrhea was severe and there was also an irritative cough. The nasopharyngeal culture on this day showed a heavy growth with a few colonies each of beta hemolytic streptococcus, H. influenzae and hemolytic Staphylococcus aureus. With the four days of treatment the course was somewhat favorable, the nasopharyngeal culture showing only a few organisms, the hemolytic streptococcus and H. influenzae disappearing entirely, and the symptoms being slightly less in evidence.

With cessation of sulfadiazine treatment, however, the hemolytic streptococcus returned and type 20 pneumococcus appeared in increasing numbers. At the same time the symptoms became aggravated and the patient developed a severe sinusitis and bronchitis. The suggestion in this case is that if therapy had been continued for a longer period the secondary infection would have been prevented.

Fig. 6 (J. L.).—Patient was treated late in his infection with sulfadiazone. Excellent clinical and bacteriologic response.

Fig. 7 (B. P.).—This patient shows excellent clinical and bacteriologic response to sulfadiazone but rapid reappearance of bacteria after discontinuance of the drug.

COMMENT

This study affords evidence that the sulfonamides do not shorten or alter the course of the uncomplicated cold. Furthermore, no striking benefits from sulfadiazine therapy were observed in the complicated colds. There is evidence, however, largely from the bacteriologic findings, that in selected cases secondary infections may be prevented by the oral use of sulfadiazine.

Our bacteriologic study revealed a consistent reduction in total organisms and number of pathogens cultured from the mucous membrane of the upper respiratory tract both in healthy persons and during colds following 1.0 Gm. of sulfadiazine three times daily. Cultures were made from the nasopharynx, which has the advantage of being relatively free from nasal and mouth contaminants, but what is true for the nasopharynx must be true also for other parts of the upper respiratory tract such as the trachea and sinuses. Bordley and his collaborators have reported similar bacteriologic findings following the local use of sulfadiazine, but their records indicate that satisfactory results are obtained only when the application is frequent enough to give an appreciable absorption. It would appear from our studies that the oral use of sulfadiazine is more dependable and simpler to administer than local application of the drug. Furthermore, the oral method is probably no more hazardous.

A very important factor in determining the value of sulfonamides in this field of therapy is the toxicity of the drug used. Sulfadiazine in the low dosage used in this experiment gives a satisfactory blood concentration but shows little clinical toxicity. The blood levels of sulfadiazine following the 3.0 Gm. daily dosage varied from 3.4 to 10.5 mg. per hundred cubic centimeters with an average of 6.9 per cent. No serious toxic reactions occurred during the study. There was no nausea or vomiting, but there were mild renal reactions, one with slight flank pain and many crystals in the urine, and the other with mild pain in the lower part of the abdomen radiating to the scrotum, with a few red blood cells in the urine. One other patient showed a sudden drop in the white blood cells at the time the sulfadiazine therapy was completed, but a few days later the blood count was normal.

The evidence from this study and other studies is that toxic reactions on this dosage of sulfadiazine are rare but that...
they can occur and must be guarded against. There is also the possibility of minor chronic pathologic changes occurring with sulfonamide therapy that may become significant following repeated courses of treatment. Finally there is the possibility of creating sulfonamide resistant organisms, a condition which up to the present has had only a slight clinical significance in respiratory infections but which might be highly important if the sulfonamides are used in frequent short courses.

During the past few years a number of reports on acquired hypersensitivity to sulfonamide drugs have appeared in medical literature. The most recent and comprehensive of these reports is that of Longcope. It would appear quite well established that a few individuals acquire hypersensitivity to sulfonamide drugs and show their reaction by fever, skin rashes, nausea and vomiting and other manifestations. The occasional occurrence of this phenomenon presents another reason why sulfonamide drugs should not be used as a routine in the common cold.

This report is only a preliminary one, but we present it chiefly because we believe that it offers a method for further study of the sulfonamides. On the basis of our experience we would restrict the use of the sulfonamides to a very few selected cases, such as those in which the history reveals an almost invariable and severe secondary infection following the cold. For example, there are the cases of asthmatic bronchitis, pneumonia secondary to bronchiectasis, repeated otitis media or recurrent severe sinusitis in which sulfonamide drugs under similar control should be thoroughly tested.

SUMMARY

1. Seventy-two colds in 66 different persons were followed clinically and bacteriologically; 48 received sulfadiazine 3.0 Gm. daily by mouth for four days, while 24 served as controls.

2. Following sulfadiazine, the nasopharyngeal flora as observed by serial cultures showed a uniform decrease in total number of organisms and a check in the growth of pathogens.

3. The clinical course of the treated colds showed no striking difference from that of the controls; however, there appeared to be some amelioration of symptoms due to control of secondary bacterial infection.

4. As a result of this study, we are opposed to the routine use of sulfonamides in the treatment of the common cold but would favor their use in a few selected cases as a protection against severe secondary infection.

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FEVER THERAPY IN OPHTHALMOLOGY

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One of the more recent developments in ophthalmic therapeutics has been the use of fever therapy for acute lesions of the eye and its adnexa. The pyrexia has been produced by three methods, the parenteral injection of nonspecific proteins, the use of malaria and physical means. There are many reports in the literature of the use of fever therapy in ophthalmology. It seems worth while to review the subject in an attempt to evaluate the various methods and to determine the safest and most efficacious one. It would appear that several of the methods have a more or less specific place in the ophthalmologist's armamentarium.

The use of fever therapy, according to Gifford, began with observation of the beneficial effect of intercurrent infection with accompanying fever in various diseases. Only recently Reginis and Delaneo and Sedan observed definite improvement in trachoma following pneumonia, typhoid and malaria. Cases have also been observed in which the use of diphtheria antitoxin produced an apparently beneficial effect in diseases other than diphtheria. Such observations in the past formed the basis on which fever therapy developed.

The mechanism of the beneficial effect of this therapy has been described recently by Sanders. He pointed out that in fever therapy a prompt effect is exerted on the autonomic nervous system; in the splanchic area a vascular dilatation takes place, with contraction of the peripheral vessels causing a chill. This is soon followed by a capillary dilatation. With the rise of temperature there seems to be a general stimulation of cellular activity as shown by the changes in the blood. There is a short period of leukopenia followed

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