linase. The data reported here give no direct information on this point, but the variety of curves obtained when resistance to penicillin is plotted against regular increases in the number of cells in the inoculum suggests that the phenomenon may have a complex basis. That this rule may not always hold is suggested by the fact that one organism, resistant to penicillin and capable of producing penicillinase showed only a slight difference in apparent sensitivity in the 2 tests. Further work on this line is now in progress.

On the other hand, that in regard to this character there are 2 sorts of staphylococci seems apparent. It is of considerable importance clinically that the great bulk of the organisms fall in the group against which the antibacterial action of penicillin is exerted with little regard to the actual density of the bacterial population.

Conclusions. 1. The action of penicillin *in vitro* against most strains of Staphylococcus is related only in a minor degree to the number of bacteria present. 2. In a not inconsiderable group of strains, somewhat more resistant to penicillin than the majority, the outcome of tests for penicillin sensitivity is profoundly influenced by the number of cells present.

15630

Clinical Trial of Gamma Globulin in the Prevention of Common Respiratory Diseases.

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Serum gamma globulin, separated and concentrated by chemical fractionation of normal human blood, was administered at monthly intervals to one-half of a group of 70 students throughout the respiratory disease season from October, 1945, to May, 1946. The incidence of acute respiratory disease, including whatever the individual considered as a "cold" of any degree of severity was carefully tabulated in the entire group.

The chemical fractionation of human blood plasma has made available certain fractions of globulin which appear to contain many specific neutralizing antibodies. Its value in the prophylaxis of measles[1,2] is now common knowledge in spite of the fact that it is still impossible to measure the concentration of measles protective substance directly. The potency of Fraction II (largely gamma globulin) was shown by Enders[3] in the case of neutralizing antibody for influenza A virus to approximate that of sera taken during early convalescence from the disease. Its protective value in clinical trial studies has not been demonstrated to our knowledge. The subjects in our study passed through an influenza epidemic but the numbers in both groups contracting the disease in a clinically recognizable form were so small in each that no conclusions can be drawn as to its prophylactic value in this instance. Enders[3] found Fraction II to contain antibodies reacting with diphtheria toxin, streptococcal erythrogenic toxin, influenza A virus, mumps virus, and the H antigen of *E. typhosa*. These antibodies he found to be concentrated from 15 to 30 times in the fraction as compared to pooled plasma. From pools of plasma obtained from several areas throughout the United States, a satisfactory degree of uniformity between the various preparations was demonstrated.[3] The gamma globulin used

[1] Ordman, C. W., Jennings, C. G., and Janeway, C. A., *J. Clin. Invest.*, 1944, **23**, 541.

[2] Stokes, J., Jr., Maris, E. P., and Gellis, S. S., *J. Clin. Invest.*, 1944, **23**, 531.

[3] Enders, John F., *J. Clin. Invest.*, 1944, **23**, 510.

in the present study was furnished on request by the Cutter Laboratories.

Clinical trials of gamma globulin are probably the most practical method of evaluating its direct prophylactic effect. This study was undertaken primarily to determine whether or not the concentrated gamma globulin contained some protective substances against common respiratory diseases. Our previous studies[4,5] indicated that prematurely born infants were much more susceptible than full-term infants to an epidemic respiratory disease presumably caused by a pneumotropic virus. There was also some clinical evidence that pooled adult serum and gamma globulin were effective in prevention or amelioration of this disease. Older children and adults did not appear to be susceptible to it. If gamma globulin could be shown to be even partially effective in preventing the occurrence of common respiratory diseases, such knowledge would indicate that man is capable of building neutralizing substances to some of these diseases. The difficulties encountered in any attempt to evaluate the many varied and undifferentiated respiratory diseases were appreciated from the outset and consequently this material is presented with tentative conclusions only.

Methods. A single class of medical students was selected because it was felt that close cooperation of the type required for the study could best be attained from such subjects. The students were living together every day in classes and laboratories in intimate association. A careful history as to their past experience with acute respiratory disease was obtained, and from these data the entire group was divided into 3 classes as to frequency of disease. One-half of each of these 3 classes was selected as experimental subjects. In October an initial dose of 6 cc of concentrated gamma globulin solution was administered intramuscularly to each student in the experimental group. Thereafter, 4 cc of the same solution was given at monthly intervals, most of the subjects receiving a total of 30 cc in 7 inoculations.

The occurrence of attacks of respiratory disease, their severity and the incidence of reactions to the inoculations as manifested by sore arm, fever or other abnormal manifestations were determined by frequent interviews with each student.

Results. In the experimental group of 35 subjects, 77 episodes of acute respiratory disease were recorded for the season. The control subjects experienced 132 illnesses during the same period. The average number of attacks per person was 2.2 in the experimental group as compared with 3.8 in the control subjects. The previous season experiences of the 2 groups are compared in Table I.

TABLE I.
Data on the Incidence of Acute Respiratory Diseases in the Experimental and Control Subjects.

	Test season		Previous season	
	Exp.	Control	Exp.	Control
Total infections	77	132	125	128
Avg per person	2.2	3.8	3.57	3.65

In the experimental group, the diseases were classed as severe in 10 instances, moderate in 17, the remainder being considered mild. Their previous season record showed that 28 attacks were considered to be severe, 38 moderate, and the remainder mild. Accordingly there was a substantial reduction in severity as compared with the previous season for this group (Table II). Not all subjects were able to classify their illnesses accurately.

TABLE II.
Data on the Severity of Infection in the Experimental Group.

Infections recorded as	Exper. group	
	Test season	Previous season
Severe	10	28
Moderate	17	38
Mild	49	46

During the 1945 influenza epidemic, 7 of the experimental subjects had influenza. This was mild in all instances. Among the control subjects there were 11 cases of influenza during the same period. One subject was hospitalized because of severity of his illness. About one-third of the students

[4] Adams, J. M., Green, R. G., Evans, C. A., and Beach, N., *J. Ped.*, 1942, **20**, 405.

[5] Adams, J. M., *Journal-Lancet*, 1945, **65**, 192.

in this study were vaccinated against influenza A and B. An analysis of those who had not received gamma globulin shows a slight reduction in the incidence of respiratory disease, but the group was too small to warrant conclusions.

Reactions consisted primarily of a sore arm at the site of the injection, lasting for one day only in most of the 26 subjects who reported a reaction. Nine reported a sore area about the site for 2 days, and 8 for 3 days. These reactions were extremely variable and recorded for the most part with the first injection only. A low grade fever was recorded in but 3 patients in the entire series and this occurred after one injection only. The highest temperature was 100°F. There were no instances of jaundice in the series receiving the gamma globulin.

Discussion. Too little is known of man's ability to produce neutralizing antibodies active against the common respiratory diseases, many of which are undoubtedly due to viruses as yet unclassified. Gamma globulin has been shown to contain many neutralizing antibodies and to have protective and prophylactic effect in certain specific diseases such as rubeola[1,2] and infectious hepatitis.[6] Our interest in the possibility that immunity might be developed against primary respiratory disease had its origin in the observation that prematurely born babies were much more highly susceptible to a specific respiratory disease than were normal full-term infants.[4] In addition we have never observed the specific disease referred to in older children or adults, at least in the form of pneumonitis. Unpublished evidence indicates that a mother suffering from a common respiratory infection at the time of delivery, may infect her offspring and the baby may show definite clinical and X-ray signs of pneumonitis shortly after birth. This fact is well established in the case of measles (rubeola). It has been shown that passive transfer of antibodies to the fetus probably takes place largely during the last few weeks or months of pregnancy. The immature fetus is much more susceptible to certain viruses than the full-term baby, as has been successfully demonstrated in animals in the case of influenza virus.[7,8]

A study such as that reported here needs to be repeated with a much larger group. Nevertheless it seems possible at present that preliminary clinical trials such as this may throw some light on a question concerning which we need more information, namely, the degree to which man is able to form neutralizing antibodies to some of the common respiratory diseases. Yannet and Deutsch[9] report failure in a group of 25 patients who developed an unknown epidemic respiratory disease (influenza-like) after having received but one prophylactic injection of gamma globulin. No mention is made in their report as to the severity of the disease in the patients receiving gamma globulin as compared with those who did not receive it. They state, "That there proved to be no evidence of prophylactic value of gamma globulin for this type of respiratory infection is not surprising." On the contrary, it seems surprising that there was not some evidence of prevention from concentrated gamma globulin obtained from a large pool of donors, if the disease they were dealing with was a common and not a rare respiratory disease. The possible advantage of repeated monthly injections as employed in the present study is an interesting point about which to speculate. The accumulative effect of passive transfer of antibodies may be important in a disease to which man may form a partial degree of temporary immunity. In our study the majority of the infections were recorded in the first half of the season as opposed to the last half. This fact may be due entirely to the epidemic character of respiratory diseases. We hope to be able to follow this approach to the problem of immunity in this obscure and difficult group of diseases further.

Summary. Concentrated gamma globulin

[6] Stokes, J., Jr., and Neefe, J. R., *J. A. M. A.*, 1945, **127**, 144.

[7] Woolpert, O. C., Gallagher, F. W., Rubinstein, L., and Hudson, N. P., *J. Exp. Med.*, 1938, **68**, 313.

[8] Dettwiler, H. A., Hudson, N. P., and Woolpert, O. C., *J. Exp. Med.*, 1940, **72**, 623.

[9] Yannett, H., and Deutsch, J. V., *J. A. M. A.*, 1946, **131**, 593.

was administered at monthly intervals to one-half of a group of 70 medical students throughout a single respiratory disease season from early October to late May. The incidence of attacks of acute respiratory disease was reduced 40% in the experimental subjects as compared with the controls. The severity of the illnesses was significantly decreased in the experimental subjects as compared with their previous season experience.

The reactions to the injections were mild and consisted primarily of local soreness at the site, lasting one day in the majority of the students. No jaundice or hepatitis was observed.

The primary object of this small clinical trial of concentrated gamma globulin was not to discover a method of preventing colds, but to determine if possible, whether or not man is capable of forming neutralizing substances for some of the undifferentiated respiratory diseases. A cumulative effect of repeated injections was suggested by the results.

A statistical evaluation of the data shows a 2% or less probability of error, which would indicate that the results were significant.

15631

Effect of Types of Treatment on Development of Antistreptolysin in Patients with Scarlet Fever.*

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During the course of studies on the treatment of scarlet fever with various agents, a somewhat greater incidence of recurrent pharyngitis, with or without a scarlatiniform eruption, was noted in patients treated with penicillin as contrasted with those receiving no therapy or globulin. For this reason, a study of the antistreptolysin titer in the sera of patients with this disease treated by the 3 different methods was carried out. Although it is well recognized that there is no relation between the level of antistreptolysin in the serum and the total antistreptococcal immunity of an individual, studies of this nature are of value, however, in reflecting the response of a host to experience with the beta hemolytic streptococcus. In a similar study, Rantz, Boisvert, and Spink[1] found that the administration of salicylates, sulfadiazine, or a "short course" of penicillin had no effect on the mean increase in antistreptolysin. When penicillin was administered over a longer interval, the frequency of antifibrinolysin response was decreased and an antistreptolysin response was also observed less often in the patients in whom bacteriologic relapse did not occur.

Methods. The cases were chosen for each type of treatment alternately and without respect to the severity of their disease. One group received only symptomatic treatment, another human gamma globulin intramuscularly (1 cc per pound of body weight up to 60 cc), and a third was treated with 120,000 units of penicillin daily for 10 days. Cultures of the nose and throat on blood-heart infusion agar and in blood broth were made daily for the first week and every other day thereafter. Serums for determination of antistreptolysin titers were drawn on the day of admission and every 7 days thereafter as long as the patient was in the hospital; a minimum of 3 serums were studied in each case, the last one being obtained at least 21 days after the start of the infection. Antistreptolysin titers were determined by the method of Rantz and Randall.[2] Only a dif-

* The gamma globulin used in this study was supplied by the American Red Cross.

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1 Rantz, L. A., Boisvert, P. J., and Spink, W. W., *Science*, 1946, **103**, 352.