As to the spacing of the time between doses. We consider this of the utmost importance, for it is possible, in a case that is susceptible to vaccine treatment, to injure a patient, to neither injure or benefit a patient, or to improve a patient, all by the spacing of the doses.

After a dose of vaccine the patient's resistance is decreased—he enters the “negative phase;” soon he reacts and his resistance begins to build up till it reaches the level of his former resistance, after which it proceeds up above the line representing his original resistance for a variable degree, and near the height of this rise of resistance is where the patient should receive his next injection. If the patient receives his next dose of vaccine while his resistance is depressed below his normal, he will get worse; if he receives his next vaccine just as he reaches his former normal, he should neither improve nor get worse from the vaccine.

I have a man now who walked into a hospital in New York with a slight tenderness in one knee. They found bad teeth, extracted seven of them and made an autogenous vaccine, which they gave him once every ten days. This man became constantly worse, left the hospital six months later in a wheel chair and is still in a wheel chair, a year later. He blamed it all to vaccine and I had an awful time convincing him that he should have more vaccine. I have been giving him vaccine now for a month and he is so much improved that he has made arrangements to send his nurse home before Thanksgiving, as he will be able to take care of himself.

I haven't a doubt but that vaccine did have a great deal to do with this man's condition due to the fact that the dosage was too far apart. Ten days would mean that his positive phase had had time to drop back to his normal, and since it was not followed up, it probably dropped below his normal every time before receiving his next dose, in this way injuring him. I am giving him a full dose of stock vaccine every three days.

I find the safest, surest and easiest way to space the doses is to watch the local reaction at the point of infection and give your next dose at the time that this local reaction disappears, which is usually three

days, although I have had them take eight days.

To make a long story short, we think that stock vaccines should be used in all chronic cases where the disease continues, but in a less active state, and that autogenous vaccines are indicated in acute cases where each exacerbation is as active and pronounced as the previous one.

Dr. Holland's paper was discussed in connection with Dr. Lyons'—discussion follows Dr. Lyons' paper.

THE VALUE OF TRIPLE TYPHOID VACCINE IN CIVIL AS WELL AS MILITARY LIFE*

BY RANDOLPH LYONS, M.D.,
New Orleans, La.

The prophylactic value of antityphoid vaccination needs no defense at the present day and all civilized nations have universally adopted this important measure. One has only to review the history of antityphoid vaccination in our own Army to appreciate what it has meant in the elimination of typhoid, even allowing full credit for improved sanitation. That this latter factor was not the only element in the successful prevention of typhoid was demonstrated recently on the Mexican border. Here there was no typhoid among the troops, but according to Chamberlain,¹ over 250 cases of paratyphoid infections with one fatality. The reason appears quite obvious—the troops had been protected by inoculation against typhoid but not against paratyphoid. Etiologically, the paratyphoid infections are transmitted in much the same manner as typhoid, with the possible exception of the meat-poisoning group, and general hygienic measures applicable to typhoid hold good for paratyphoid. From this it seems reasonable to conclude that in order to eradicate the typhoid-colon group of infections it is necessary to protect the individual not only against the typhoid but the paratyphoid organisms as well. This means the use of a vaccine containing the

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typhoid bacillus and the paratyphoid bacilli "A" and "B"—a mixed triple vaccine. Such a vaccine has of late been recommended for our Army and is advocated by Craig² and others. In this country it would seem that until recently the importance of paratyphoid infections has been underestimated in military and especially in civil life.

France, England and Japan, according to reports in the literature, have learned this lesson and are employing preventive inoculations, containing all three organisms, among their forces.

The question whether or not such a triple vaccine should supplant the ordinary antityphoid vaccine in civil life is the point to be discussed.

In 1911, in a paper¹ on paratyphoid fever and its prevention, I advocated the use of a triple vaccine against typhoid and the two paratyphoids because of the prevalence of the typhoid-colon group in my community. At that time I was unaware of Castellani's³ work along this line. He first tried out such a vaccine in India and states in 1909 that such a vaccine had been made use of in Ceylon since 1905. His vaccine consisted of 500 million typhoid bacilli and 250 million each of paratyphoid bacilli "A" and "B," respectively, to the c. c. The first dose was .5 to .6 c. c. and the second or third dose 1 c. c. to 1.2 c. c. Kabeshima,⁴ in 1912 and later in 1914, reported on the extensive use of a combined vaccine of typhoid and paratyphoid "A" and "B." During the period from 1909 to 1911 he inoculated about 12,000 men with remarkably good results.

Since this time many advocates are to be found in this country, England and France. The vast majority of these, however, are army and navy surgeons. The importance of such a preventive measure in civil life seems to have been almost completely overlooked. This is probably due in part to the lack of statistics in our cities in regard to the actual percentage of paratyphoid infections. There are still too many practitioners who seem to think that paratyphoid fever is a rare condition. This can be accounted for by the fact that the diagnosis of typhoid is too often simply based upon clinical symptoms rather than from blood cultures and serological

tests and also because many boards of health classify the paratyphoid infections under the head of typhoid.

Another factor which militates against the universal employment of such a vaccine is the prevalent opinion that paratyphoid infection is so mild that it is hardly worth while bothering about. It is obvious, then, that as long as such conditions and opinions exist the value of protection against all three diseases simultaneously will not be fully appreciated. It is, therefore, justifiable to examine briefly into the facts.

Some years ago in New Orleans, while making routine blood cultures on supposedly typhoid cases, I found the proportion of paratyphoid infections to be 8%. Some of my colleagues have considered this estimate too conservative; nevertheless, this is by no means an insignificant proportion. As this community has fewer enteric infections than many cities of its size, it is fair to assume that other communities would have the same proportion of paratyphoid infections, or possibly higher if the subject was investigated statistically.

While it is quite true that on the whole the paratyphoids are milder and of shorter duration than typhoid, when we consider the mortality and complications, we find them deserving of more respect. In my own experience I have had a case of paratyphoid run fever for over two months, and another case, which I reported, developed a cholecystitis caused by the same organism, which necessitated surgical interference. Carles,⁵ in France, reports 170 cases of paratyphoid infection, 63 of whom had fever 20 to 30 days; 38, from 1 to 7 months; 2, for 3 months, and 1, for 4 months. Sixty-six had fever for 6 to 20 days only. Relapses occurred in a little over 12% of these cases; there were 8 deaths, or 4.7%. Rimbaud⁷ obtained positive blood cultures in 355 out of 730 cases of apparent typhoid. One hundred and ninety-four of the cultures were paratyphoid (138 Para "A" and 56 Para "B"). The mortality in the paratyphoid infections was 4.6%. He states, however, that an attack of paratyphoid incapacitates a man for military service for three months at least.

Pathologically, the causes of death in 16 cases of paratyphoid infections examined by Dawson and Whittington⁸ were found to be: perforation, 2; peritonitis, 2; hemorrhage, 2; hemorrhage and toxemia, 3; toxemia, 4; pneumonia, 2; splenic abscess, 1. These 16 necropsies represented a mortality of 4%. Many other reports in regard to the pathology and complications of the disease could be appended if time permitted.

A further objection against the use of the mixed vaccine is one that Castellani had to answer some years ago. He says: "The usual objection raised against the use of the mixed vaccine is that it will probably give a much smaller amount of immunization than the simple typhoid vaccine and that paratyphoid 'A' and 'B' being diseases of less importance than true typhoid, it would be a mistake to run such a risk. This belief is not supported by my experiments." Upon individuals he found that those inoculated with the triple vaccine developed for each germ almost the same amount of agglutinins as those inoculated with each germ separately. This observation has very recently been borne out by Craig,⁹ who concludes that such a vaccine gives as good results in immunization as far as can be judged by agglutinin curves as does the typhoid inoculation and that neither the general nor the local reactions differ in any degree from the inoculation with simple typhoid vaccine. The results, both from a practical and theoretical point of view, are all in favor of combining the three organisms in a single vaccine.

Craig employed a vaccine of higher strength than Castellani. It contained a 1,000 million typhoid and 750 million paratyphoid "A" and 750 million paratyphoid "B" bacilli per c. c. The first dose was 0.5 c. c. and the second and third doses each 1 c. c. This should prove an effective dosage.

In my early work I employed a vaccine containing equal numbers of all three organisms in a strength of 2,000 million organisms per c. c., or in round numbers, 700 million typhoid, paratyphoid "A" and paratyphoid "B," respectively. During the past two or three years I have used the mixed vaccines put up by biological

houses. Most of these contain 1,000 million typhoid organisms and 500 million each of paratyphoid "A" and "B" to the c. c. The first dose is .5 c. c. and the second and third doses 1 c. c. each.

It would be advisable should the Government adopt such a vaccine as Craig suggests, that biological houses put upon the market one of similar concentration in order that comparative results might be obtained.

In my experience with the triple vaccine I have found it advisable to begin with .25 c. c. for the first dose, advancing the dosage to .5 c. c. for the second and 1 c. c. for the third dose. In civil work this is a good plan, as many individuals are discouraged from taking their second and third doses if they happen to have some reaction with the first dose. During the past six years I have inoculated over 150 individuals with the mixed vaccine. Of these I have been able to follow 50 from periods of one to six years. Those inoculated during the past year have not been considered in this report. None of the 50 individuals mentioned have developed any infections of enteric type. My own blood was examined a few weeks ago by Dr. F. M. Johns, who found that it still agglutinated *B. typhosus* up to 1/100 dilution in forty-five minutes, but no longer agglutinated paratyphoid "A" and "B." This is quite an unusual reaction after a lapse of over six years and possibly depends upon the fact that my last dose was a large one containing 1,000 million of each organism. This brings out an interesting point that while the dosage of each organism was the same the highest agglutination titre was always against *B. typhosus*.

In civil practice a vaccine containing a greater number of typhoid organisms is the one of choice. Such a vaccine can not be considered as a shotgun preparation, as the organisms belong to the same family group and group-immunity factors probably play a part in enhancing the immunity against *B. typhosus*.

It should be recalled that paratyphoid "A" and "B" are not the only intermediates between the typhoid and colon organisms. Occasionally a "gamma" or other intermediate is isolated, but these

are so rare as to be negligible and are of no practical importance.

The advisability of adding other organisms to such a vaccine, as has been suggested, such as dysentery, cholera, etc., is of questionable merit. It would undoubtedly tend to reduce the concentration of the organisms present and mix unrelated groups—all of which rather smacks of the shotgun.

As regards methods of administration, intervals between doses, and dangers to be guarded against, the same rules hold good for the triple vaccine as the simple antityphoid. They are so well known as to require no comment.

In concluding, a word should be added in regard to the mixed typho-serobacillins. It is claimed that they produce a better and more rapid immunization with less local and constitutional reaction. It is too early to make predictions in regard to the lasting quality of the immunity obtained. At the present time their high cost and somewhat questionable superiority will prevent them from coming into general use. My experience with this type of vaccine has been obtained with the product found on the market and limited to 15 cases. These individuals for one reason or another required rapid immunization and the injections were administered every other day. Among this small group the local and general reactions appeared to be somewhat less than with the ordinary triple vaccine, but the number is too small to warrant any deductions.

CONCLUSIONS

1. Paratyphoid infections are more common than generally supposed.

2. The disease has a death rate of from 1 to 4% with much the same complications as typhoid.

3. Practitioners should corroborate the clinical diagnosis of typhoid with blood cultures or serological tests in order to differentiate typhoid and paratyphoid infections.

4. Boards of health should classify typhoid and paratyphoid infections separately in order to determine the relative prevalence of paratyphoid infections in a given community.

5. A mixed triple typhoid vaccine gives ample protection against typhoid, at the

same time protecting the individual against paratyphoid "A" and "B." It should supplant the simple typhoid vaccine in communities where paratyphoid infections exist.

6. If such a vaccine were generally employed in civil life the morbidity from fevers of unknown origin and many so-called typhoids with negative bloods would be greatly lessened.

7. In military life such a vaccine is rapidly becoming a necessity.

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DISCUSSION

Papers of Drs. Holland and Lyons.

Dr. J. E. Paullin, Atlanta, Ga.—Many of us have wondered in times past why some of our patients who had received prophylactic injections of bacillus typhosus a few months subsequently developed clinical typhoid fever, and we were tempted to ascribe the development of that disease to an inefficient typhoid vaccine.

During the past year we have had in Georgia a small epidemic of paratyphoid infection, which occurred in quite a few instances in individuals who had previously received prophylactic doses of bacillus typhosus. While it is true that there are coagglutinins between the bacillus typhosus and paratyphoid organisms, at the same time prophylactic injections of the bacillus typhosus do not furnish any immune substance to para "A" or para "B" organisms. The only way of telling whether you are dealing clinically with infection of bacillus typhosus or paratyphoid "A" or paratyphoid "B" is by blood cultures, and the only method of preventing the development of these diseases is by the prophylactic injection of a combined or triple vaccine. Blood cultures made within the first week or ten days of the disease will very clearly differentiate the larger organisms one has to deal with, and many ill effects or lack of efficiency which has been previously ascribed to prophylactic injections of typhoid vaccine, are due to the fact that the individual who subsequently develops infection has

not developed typhoid, but has developed infection with paratyphoid "A" or paratyphoid "B." Para "B," I am inclined to think, is a very common disease, and it is only within the past year or so that the profession as a whole has begun to differentiate between the infections with the various organisms. Every fever which ran a more or less continuous course, with the usual symptoms of typhoid fever, as Dr. Lyons has well pointed out, has been classed as typhoid fever, and in rural districts particularly, where such an infection did develop, immediately prophylactic injections of bacillus typhosus were given. These, of course, did not protect against the para infections, but in this particular epidemic, which happened during the summer, where the infection was altogether with para "B," as soon as prophylactic injections were instituted of para "B," instead of going ahead and giving bacillus typhosus, it was only a matter of a short time, together with the usual sanitary measures to control the spread of the disease, that the infection was soon under control.

I think Dr. Lyons has brought to our attention a subject which is of a great deal of importance, and one which will have more consideration from those of us who are interested in preventing this infection.

Dr. E. C. Thrash, Atlanta, Ga.—A number of years ago, in the administration of vaccines, I felt very much less enthusiastic in these agents as a cure and much more enthusiastic over vaccines as a preventive.

We have the best illustration of the preventive effect of vaccines in the work that has been done with the typhoid germ, with its concomitant or allied germs, and we get an illustration of this lack of efficiency as a curative measure in our efforts to cure diseases with autogenous vaccines.

There is a field, in my opinion, for vaccine prophylaxis, and I believe we will come to use less and less vaccines as curative measures. Foreign proteins produce an increase in the cellular substance of the blood, and no doubt establish resistance in a measure in a non-specific way; but when we attempt to make a specific remedy from autogenous vaccine, unless we grow these vaccines in pure cultures from the blood, there are ten chances to one that we get a germ concerning whose pathogenicity we do not know, and we inject a lot of substances which are nothing more nor less than foreign proteins.

I believe that ultimately vaccines for curative measures will be given in the form of an indifferent protein with a specific vaccine that is producing disturbance. This can be obtained by bouillon filtrates, and we get a foreign protein from the bouillon filtrates, and the specific toxins in the filtrate are eliminated; they are by-products of the growth and have no bearing upon the disease.

I have been impressed particularly in the administration of tuberculous vaccines. If we get a case of tuberculosis with a fairly high degree of resistance we can immunize that patient with tuberculin, and we do apparently employ a curative measure, but we establish immunity as in typhoid fever. But if a patient is profoundly

toxic and the disease is advanced, our attempt at vaccine therapy is worse than futile. Our measures only accomplish results in producing immunity in a person in whom it has already been fairly developed.

Dr. W. L. Dunn, Asheville, N. C.—Why is it that we have two different views in regard to vaccine therapy, one of which is the wholesale condemnation of vaccines and the other is favorable to their use? There must be some explanation for both. One explanation is that very often some good results are obtained from the use of vaccines, and the other is that there have been a great many negative or bad results. It seems to me that every one who has used autogenous vaccines has been struck in individual cases with the marvelous results obtained, whereas in a number of cases the results secured are absolutely negative.

Rather than condemn the use of autogenous vaccines, we must seek for an explanation either in the method of their administration or in the preparation of them. We have used them rather extensively and have been impressed with the marvelous results secured in a certain number of cases, and I feel that while we are condemning so vigorously stock vaccines, we must remember that our methods of production of autogenous vaccines are by no means good nor well worked out. There seems to be some place where we are at fault. Perhaps it is in culturing the organisms on individual media and reculturing them to get pure cultures for our vaccines.

After all, there seems to be something in vaccine therapy in isolated cases, and we should look to our methods of preparation and methods of administration before we condemn vaccines in a wholesale manner.

Dr. Deering J. Roberts, Nashville, Tenn.—I beg leave heartily to add my endorsement to vaccine therapy. Vaccine therapy is but an added lustre to the great renown of the immortal Jenner. Jenner used autogenous vaccine when he took the pus which contained serum from the udder of a cow. Vaccine therapy has done wonders not only in smallpox, but see what it has done for diphtheria! See what it is doing in tetanus! It is one of the brightest crowns belonging to progressive medicine. While it started a long time ago with Jenner, we are getting further and further along and have not yet reached the climax of its efficiency. We have to study a little more, work a little harder, apply the eye to the lens a little more, and use more coloring reagents to differentiate between the different etiological factors concerned in the various diseases before us.

With reference to paratyphoid, I regard it as a misnomer. Paratyphoid is a duplication of the name. Paratyphoid, like typhus, was considered and known a decade and a half ago. About that time we had an epidemic of what we now know as typhoid fever in the City of Nashville. Cases developed in the summer and the disease extended well on into the winter, and it was certainly an epidemic. Some physicians called it typhoid. We had cases in the early stage of what was thought to be a new disease as I called it then, because I had not seen it develop in such numbers

before. However, it was called typhoid because in the early stages there was more or less constipation. The intestinal tract of these patients was loaded with cathartics; they went on for eight or ten days or two weeks and then were turned over to the undertaker to hide the mistakes. I read a paper before the Tennessee State Medical Association at that time entitled "Fever—Just Fever," because that was all it was. These patients did not have any intestinal trouble. I had no case that lasted over two weeks which did not belong to typhoid fever. I simply let these cases alone. Of course, I had to give them some medicine. I resorted to a placebo. People will take drugs when they won't take advice. I put these patients on six drops of dilute phosphoric acid every six hours; that gave the nurse and family something to do. It did not harm them. Of the mineral acids, perhaps phosphoric acid is the best to stay tissue waste. Later on, as time passed, the microscopists got to work and now we have paratyphoid, which I regard as a misnomer.

Again, I wish to say, all hail to Jenner and to his successors for doing so much today in regard to vaccine therapy!

Dr. Lyons (closing).—I have nothing further to say except to emphasize the point Dr. Paullin brought out, that we should pay more attention to paratyphoid infections. Another point he has brought out has been mentioned recently by a number of English observers, that cases that have been vaccinated against typhoid were having typhoid fever again within a comparatively short time. When these cases were studied intensively by blood cultures and careful serological tests, they were found not to be cases of typhoid but of paratyphoid. Had these tests not been made, these cases would have gone down in medical literature as having had typhoid, after having been vaccinated against the disease, to the discredit of anti-typhoid vaccination. By making a careful diagnosis of our cases into proper groups, and by the use of a triple vaccine, we will not have so many cases of that type, and the credit of anti-typhoid vaccination will be maintained.

THE NATURAL STARTING POINT OF ALL RATIONAL MEDICAL THOUGHT*

By J. C. JOHNSON, M.D.,
Atlanta, Ga.

This day is full of meaning for us, not merely as an event, but because of its opportunities and its obligations. Its opportunities are as broad as we may see fit to make them. Its obligations are as serious as is the purpose of our organization. The purpose of our organization is to give to

gastro-enterology the recognition it deserves, to enlarge its usefulness, to increase professional efficiency and serve the common good. To this end, we shall devote our energies and invite the co-operation of all who have like desire and like determination.

As yet our number is small, because as is the case in every movement, some few have undertaken the initiative and have endeavored to develop plans by which the Association may be well established and its interest best conserved. The ideals of membership have not been conceived in estimate of our own achievements, but in what we believe this work demands and what it promises for its well doing.

The task before us is not a little one. There will be many difficulties in our way and doubtless much discouragement. But if we do our duty it is reasonable to expect that the Association will grow in size, in strength, and in service.

By your courtesy I am allowed to extend my opening remarks. This I wish to do in a general way instead of confining myself to the formality of a single topic.

It is always agreeable to enumerate our virtues and successes, and of each of these the profession has very many. But it is more profitable to acknowledge our deficiencies, to recognize if possible the cause of them, and try to overcome them. With highest appreciation, this is the view I wish to take this morning.

Medicine, as a science, is the same today that it has always been, and so it will remain throughout all efforts to unfold it. As an art, it is more elaborate; it has changed from time to time, and is still in process of evolution.

Though our facilities have increased and our methods have improved, practice is more laborious and results are yet very far from what they ought to be, considering the cost to the public and the time and energy expended by the profession. This is not the fault of medicine itself, nor altogether the fault of the profession. We find more to do and are able to do it better, but obstacles have increased proportionately. The laity have gathered a small and spurious knowledge of disease from current magazines and the daily press which, instead of enabling them to under-

*President's Address, Southern Gastro-Enterological Association, Memphis, Tenn., Nov. 12, 1917.