12. The amount of these ferments in even the best serums is relatively small and the serums must therefore be used in larger doses than has been customary in the past.

13. Anti-meningococcic serum is both anti-bacterial and antitoxic.

14. Since the efficiency of curative serums is increased many fold when administered intravenously, this route will be used more frequently than has been the custom in the past.

A CONSIDERATION OF AUTOGENOUS VACCINES.*

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Empiricism is dying. Throughout the last century and particularly its latter decades, the searchlight of truth has lighted up many of the heretofore dark places in the study and practice of medicine. The discovery of the causation of many diseases through bacterial agencies was epoch-making and led the way naturally toward the introduction of measures able to cope with such a foe.

During the last thirty years scores of men have been at work on this problem and have each added their little to the sum total of our present knowledge and from the time of Jenner one startling etiologic and therapeutic discovery has followed another, so that among the names destined to live will always be found those of Pasteur, Koch, Pfeiffer, Ehrlich, Behring, Wassermann, Nogouchi and others.

Bacteria are divided into two classes, the good and the bad—Saprophytic and Pathogenic. The Saprophytic bacteria are scavengers; they thrive best on dead tissues and assist in freeing the body of many waste products. Pathogenic bacteria thrive best on the living tissues of the host in whom they are capable of producing disease. Their pathogenic action is due to the liberation of the toxins they contain or the elaboration of poisons in the tissues of the host.

Of these bacterial toxins there are two main types: The Exo-toxins, contained in bacteria whose poisonous principles are capable of being dissolved out of the bacterial cell. To this class belong the Bacillus of Diphtheria and the Bacillus of Tetanus. The great majority of bacteria, however, produce Endo-toxins, or poisons which are incapable of separation from the cell bodies by any of our known filtration methods. Examples of this are the Bacillus of Typhoid Fever and the Streptococcic and Staphylococcic groups.

While bacteria are capable of producing disease it is not through their mere presence *per se,* for as we know, our persons in health permit of the culturization of numerous pathogenic bacteria, therefore, other factors must enter in and these factors comprise the natural defensive mechanism of the body against disease.

Natural Resistance: This varies greatly with the individual and has a certain selective action, for why is it that one person can harbor in his mouth virulent Pneumococci and Streptococci and yet can go through life without a single attack

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of pneumonia and, conversely, be subject to repeated attacks of tonsillitis, whereas, another individual harboring the same organisms may have several attacks of pneumonia during his life time and none of tonsillitis. This is due to the development of what we call *immunity,* which is the power of resistance the body tissues are capable to exert against bacterial poisons. *Immunity* may be divided into *species* and *racial immunity.*

Species Immunity: It is well known that many animals are naturally immune to disease common to man and that it is only with the greatest experimental difficulties that infections with these diseases can be made successful.

Racial Immunity: Also among the different races of the same species there appears to be a natural immunity against certain diseases, which have long been prevalent in that particular section, and which when carried to another section where fresh soil is obtained immediately light up into virulent epidemics. This is seen in the ravages of tuberculosis among the Negroes and the American Indians, and it is seen conversely in the immunity from yellow fever that has long been enjoyed by the Negro.

Acquired immunity is the protection that is afforded an individual who has passed through an attack of one disease, this conferring a greater resistance to that disease in the future. This is commonly observed in diseases like typhoid and yellow fever. Acquired immunity may be either active or passive. The process of conferring protection by treatment with either an attenuated form or a sublethal quantity of the infectious agent of a disease or its products, is spoken of as "Active Immunization," because the immunized individuals gain their power of resistance by taking an active physiological part in the acquisition of this new property of "Immunity." Thus active immunity can be acquired by repeated injections of attenuated cultures, as in Pasteur's work in hog cholera; by injections of sublethal doses of virulent bacteria as demonstrated in the protozoon disease of Texas fever; by injections of killed bacteria, first suggested by Chauveau. This method of active immunization with gradually increasing doses of killed bacteria, has been carried out successfully against many bacterial diseases. It is particularly useful against those groups of bacteria producing Endo-toxins and finally by injections with bacterial products from poisons excreted or liberated from the bacterial cell body. These measures comprise *vaccination.*

Passive immunity, on the contrary, is that gained by the host through no active formation of anti-bodies on its own part, but rather accepting ready to hand the anti-bodies prepared by the tissues of another species. The most conspicuous types of this are the anti-diphtheritic and anti-tetanic sera. These are both designed to meet bacterial exo-toxins and it is this type of sera that is most successful. On the contrary anti-gonococcic, anti-streptococcic sera and the like, which depend for their activity on the lysin, opsonin and other anti-bodies they contain, are not blessed with a like therapeutic success. Allen states that "these sera are not always curative, indeed, their use during active disease may not be altogether free from danger. Thus the administration of anti-cholera or anti-typhoid serum, which each depend for their activity on the lysin they contain, may result in the extra-leucocytic lysis of so many bacteria that the resultant

flooding of the tissues with large quantities of their contained endotoxin may imperil the life of the recipient from the additional toxaemia."

Bacteria have a selective action, not only must they gain access to the body in large enough numbers and possessing sufficient virulence, but they must also gain entrance to a tissue that is suitable for their further development. For instance, you can rub a typhoid culture into an abraded surface of the arm or a culture of streptococci can be swallowed, both with equal impunity, but reversing the conditions a bacterial infection is sure to follow.

Now what are the general defenses of the body against this bacterial invasion? They are fourfold:

1. *Antitoxins,* or substances manufactured by the tissues which are capable of neutralizing the soluble toxins produced by certain groups of bacteria.

2. *Agglutinin,* a substance which causes bacteria free in the tissues of blood stream to be clumped together in masses and held nearly immovable and therefore more accessible for phagocytosis. This is the more conspicuous where it concerns the motile bacteria. Though originally observed in 1889 by Charrin and Rogers, in studying the Bac. Pyocyaneus, the agglutination reaction is commonly associated with Widal, who first applied the phenomenon in the diagnosis of disease by an unknown organism.

3. *Lysin,* a substance or substances elaborated by the body which has the property of dissolving certain bacteria. Pfeiffer noted that guinea pigs which had been immunized against cholera bacilli could withstand the intra-peritoneal injection of further virulent cultures without harm and found that the peritoneal fluids dissolved the organisms.

4. *Opsonin,* discovered and named by Wright, is a substance that prepares or sensitizes the bacteria for ingestion by the phagocytic elements of the white blood corpuscles.

There are two types of bacterial infection, local and general. The former is best represented by boils, the latter is seen in diseases like typhoid fever, pneumonia, puerperal sepsis and the like. When a person recovers from a bacterial disease like typhoid fever, it is by the body having gradually elaborated the foregoing anti-toxins, agglutinins, lysins and opsonins in amount sufficient to cause the neutralization, destruction and solution of the bacteria. The time required in the manufacture of these substances varies in different diseases, 21 to 28 days, as a rule, in typhoid fever; 9 to 11 days, as a rule, in pneumonia, etc. So we have two biologic methods of treatment, serum and vaccine treatment, and the principle of the former is to supply these protective substances ready made (passive immunity), and in vaccination to stimulate the tissues to reproduce them more quickly, and, in as much as diseased tissues are more sluggish, in locally manufacturing them, to utilize or exploit healthy tissues for the advantage of the enfeebled ones. This then is the scientific basis for the action of vaccines. And now what are vaccines?

Vaccines are emulsions of the bodies of dead bacteria killed in various ways and suspended in suitable dosage in a solution of normal saline.

There are two types of vaccines—heterogenous and autogenous. Heterogenous vaccines are prepared from infections similar to the case which is to be

treated, but from infected material not derived from the patient himself. This type of vaccine may be and usually is polyvalent; that is, cultures are obtained from several infections of the same nature, and therefore represent, possibly, several "strains" of the same organism. These heterogenous vaccines are commonly called "stock vaccines," perhaps, because they are prepared in quantities and held in readiness to be used in a given case on demand.

Autogenous vaccines are prepared from cultures grown from infected material and obtained from the patient himself. In other words they represent, and are specifically, the organism from the effects of which the patient is suffering and toward which you are assisting the patient to establish an immunity. Knowing these differences, it is not difficult to understand that biologists, bacteriologists, serologists and clinicians of the thinking type, are agreed that the autogenous group of vaccines fulfill best the scientific therapeutic requirements. Let me quote from an article recently published by a man whose authority is unquestioned: "With the exception of certain organisms, such as tubercle bacillus and the gonococcus, there is little reason for employing stock vaccines instead of autogenous, and there is abundant ground for believing that the use of stock vaccines will not only lead to carelessness of diagnosis and misinterpretation of the probable nature of the infection, with consequent administration of the wrong species, but will sometimes be directly harmful. I am well aware that the argument has been advanced that laboratories are not sufficiently available to practitioners in all sections to make it possible for them to obtain autogenous vaccines, and would reply that, in a measure, this may sometimes be true, but the general demand for stock vaccines has been artificially stimulated by manufacturers, and the practical application of this method of treatment has out-distanced the scientific investigation of its merits. Instead of wholesome growth with the gradual provisions of local agencies where autogenous vaccines could be obtained, an unwholesome growth of this mode of treatment has been stimulated and those who seek to keep up with the latest pronouncement of advertised literature find themselves in a position of dependence upon stock vaccines in many cases. There can be no doubt that in some instances stock vaccines are satisfactory. Staphylococcus and typhoid and tuberculosis vaccines are instances, but the other forms, and especially streptococcus and pneumococcus and mixed vaccines, are of very doubtful efficacy.

"Here we come upon the field or variability in the organisms themselves and unless a growth has been prepared from the patient himself, the strain may be entirely different and inappropriate. It avails little to use mixed strains which require the reduction of dosage of the one possibly present and available strain below the point of usefulness, because of the simultaneous injection of several other strains in the mixture, which are of no use, or practically useless.

"As for stock mixture of heterogenous organisms designed for the treatment of cases in which no sort of accurate bacteriological diagnosis has been made, too vigorous condemnation cannot be phrased."

In my own personal experience I have met with many cases referred to me by other practitioners, cases on whom various stock vaccines had been tried for various lengths of time, in various dosages, with absolutely no improvement, and which have responded with surprising promptness to an autogenous vaccine

and have established an immunity that in many cases has lasted for years, and I, personally, have used in some cases stock vaccines of differing types, giving them a thorough trial, only to become discouraged at their non-success, and have discarded them for autogenous vaccines, with gratifying results.

On the other hand, I believe that stock vaccines of a single or of a polyvalent single organism type have their place, and a very important place, of usefulness in the (46-69) hour interval that if often necessary to prepare the autogenous vaccine, after the bacterial identification in the specific case has been established, and I, almost uniformly, use this period to give one and sometimes two injections of the appropriate stock culture. Appropriate stock vaccines may also be used with advantage in association with autogenous vaccines in suitable cases.

A word or two now to ensure success in getting the proper bacterial results in culture taking:—The first principle is to obtain your material free from contamination, and this requires the observance of special precautions according to the kind of material that is to be cultured.

Urines: Should always be obtained by sterile catheter, after the external meatus has been properly cleansed, and drawn off into a sterilized flask or bottle to which no preservative is to be added. It is better to catheterize the day specimen into one receptacle and the night specimen into another.

Feces: Should be obtained urine free, and specimens from first and last portion of the stool obtained and studied.

Sputum: Should be obtained with greatest care, because for practical purposes no mouth is germ free, and alveolar pyorrhœa, infected tonsils and the like are so common. Before retiring, the mouth should be carefully rinsed with sterile water and the teeth brushed with a sterilized tooth-brush, and a closed vessel containing sterile water, placed at the bedside. In the morning, the mouth should again be rinsed thoroughly with the sterile water, gargled, and with the brush re-sterilized, by dipping in boiling water, the teeth should be thoroughly brushed, and then a few mouthfuls of clean sterile water should be swallowed. After this, the sputum should be expelled by coughing and caught in serial, sterilized, wide-mouth bottles (with sterile corks). It is best that only one or two masses of sputum should be expelled into any one bottle, and the bottles labeled and sent at once to the bacteriologist for immediate examination.

The sputum should, after direct examination of stained specimens to determine morphologically the different types that may be present, be then "whipped" through several petri dishes containing sterile water, to further free the bacteria from surface contamination, and the final washed specimen planted upon the different culture-media that appears best suited for their recovery in pure culture, as judged from the findings on the first direct examination.

Cultures taken from boils or from infected sinuses, from acne pustules, from tonsillar follicles, and the like, should be made only after thorough appropriate cleansing and disinfection of surface relations, and then taken from a second or third portion of the material, discarding the first, by means of a platinum wire or a sterile capillary glass pipette inserted well within the cavity.

Cultures from eye, ear or nose should be taken with appropriate measures to ensure success.

Blood specimens should always be obtained from a vein, preferably that at the bend of the elbow, by means of an all-glass sterilized syringe of a capacity of not less than 5 cc. It is rarely, if ever, necessary to cut down on a vein, but the arm should be thoroughly sterilized by tincture of green soap and water, by 5-10 per-cent lysol, by absolute alcohol and finally by ether—personally, I prefer not to use iodine. It is better to moderately tourniquet the upper arm before sterilizing in order to prevent thin-walled veins from collapsing under the pressure. The blood should be immediately plated and flasked in peptone and dextrosed-broth.

In pulmonary abscesses, in suitable cases material may be obtained by lung puncture in the following way:—after sterilizing the chest wall in the same manner as for blood cultures, the needle attached to an all-glass syringe containing 3 cc. of peptone broth should be plunged into the lung at the proper point, as determined beforehand by clinical means, and 1 cc. of the broth introduced and reaspirated as far as possible and tubed. This measure will yield results in many cases properly selected clinically.

After getting suspected infected material, direct examination by means of variously-stained slide specimens should be made to determine morphologically and by staining reactions and relations, whether one or more types of organisms are present and if the latter how many and what types, and then, aided by this knowledge, proceed to utilize the various culture media that will best ensure recovery of each organism in pure culture. Here is where the thoroughly trained bacteriologist will succeed and in the shortest time. It is often exceedingly difficult to recover a shyly growing streptococcus or tubercle baccilus occurring in small numbers, let us say from a urine practically alive with the bacillus coli. This may be accomplished by inhibiting or attenuating the growth of the hardier, more freely growing organism, by treating the culture medium in an appropriate manner, but unless this is accomplished it will be seen at once how useless it is to successfully treat pyelitis of streptococcal or tubercular origin by using only the B. Coli in the vaccine preparation. Hence the failure of many autogenous vaccines that are bacteriologically imperfect or incomplete.

In many cases of chronic gleet, however, the gonococcus is absent, and the catarrhal inflammation is kept alive by secondary invaders which may then, in combination, serve for cure in absence of the primary invader.

After getting out every bacterial group contained in a given specimen, each in pure culture, these should then be studied with a view to ascertain their share in the production or continuation of the disease in question and guided by experience, clinical as well as bacteriological, a final judgment of the organisms concerned may be passed and the proper ones selected for use in the vaccine. They may all be combined in a single ampoule or may be placed singly or in pairs. Only the lower dosages, however, can be reached by making a mixed vaccine composed of many elements on account of the combined dosage being too high to permit of safe injection.

We can now proceed to prepare the vaccine, in which the following steps are concerned:

1. To obtain an emulsion containing the bacteria impurity—an emulsion with a uniform suspension and as free from bacterial clumping as possible.

2. To standardize the emulsion—that is to determine how many bacteria are contained in each cubic centimeter.

3. To kill the bacteria in the emulsion and tube them—or

4. To decide upon the dosage of each ampoule or set of ampoules; to tube them still alive and then kill them.

5. To label, effectively, each ampoule and place them in sets of ten in compartment-boxes or cartons, the lids of which are to be specifically marked with the names of the organisms they contain and in what dosage and, most particularly, with directions for their use.

6. To be sure that all "controls" are sterile before allowing the vaccine set to leave the laboratory for use.

I shall not, in this paper, enter in detail into the technique required in the actual preparation of the vaccine, but I want to say a word or two of caution regarding the best ways of killing the bacteria without impairing their immunizing properties. This can only be accomplished by a thorough knowledge of an observance of the thermal death-point of each group of organisms; a knowledge that will tell you which bacteria should be killed by heat, and which by chemical measures, or by a combination of the two. If by heat, at what temperature and for how long sustained? If by chemical sterilization, by what chemical and in what strength? I have known many autogenous vaccines—otherwise quite appropriately selected bacteriologically and faultlessly prepared, to be inert and to fail absolutely therapeutically, for no other reason than that the thermal and chemical death-points were not carefully ascertained. And I doubt not that this applies equally to many stock vaccines.

Have we in vaccine therapy a means sufficient to combat all types of bacterial infections? I would answer emphatically "No," and I would add that harm may often come from their indiscriminate use and from use in the hands of the inexperienced and careless.

In epidemic meningitis, in typhoid fever, in pneumonia, in generalized bacteremia, with or without ulcerative endocardial lesions, the use of vaccines for curative purposes has not been attended with great success, although, occasionally, a case is seen in which amelioration in severity of symptoms has taken place which rightfully or wrongly has been ascribed to the use of the vaccine. I am by no means yet convinced that their use in such cases is unjustifiable and believe that we may yet arrive by experience at some method of establishing appropriate dosage and proper intervals of injection for this class of acute fulminating infections that will produce better results.

The most suitable field for vaccines, and the field in which the most brilliant results have been obtained, lies in treatment of diseases, acute or chronic, that have local foci of infection, such as, furunculosis, carbuncles, abscesses, various bone diseases, such as osteomyelitis, various skin diseases, such as acne-vulgaris, infected sinuses, pyelitis, empyema, various infections of the mouth, such as pyorrhœa alveolaris, infections of the nose and nasal passages, various post-gonorrhœal conditions and various diseases of the respiratory tract, such as pulmonary abscesses.

And now a final word as to why vaccines fail in the hands of many workers, even in the above field of election—it is chiefly because of insufficient knowledge

governing the general laws of dosage and time intervals of injection; by selecting inappropriate points of injection; by disregarding the best time of day at which injection should be given, so that the patient is not protected during the "negative phase" period, at which his anti-body formation is at the lowest ebb, etc., etc. For information upon many of these points I would refer the student or interested worker, to a close perusal of monographs on this subject, notably, Allen on "Vaccine Therapy."

Finally, I would call attention to a common cause of failure from a neglect to realize that autogenous vaccines need to be freshly renewed—i. e., a new culture taken and a new vaccine prepared from cultures that represent more nearly the *status praesens* of the case, for it frequently happens that, in long chronic conditions, the bacteria by mutation or other biological properties, become adapted more or less to the anti-bodies formed in the tissues of the host.

I was asked, before reading this paper to this body, whether I did not think it quite feasible and proper for druggists to establish autogenous and stock vaccine departments for the purpose of themselves *making* these products. I do not think it is practical, nor fitting that you should, nor do I believe that the attempt would prove, commercially, a success. And I will close with the words of Sir Almroth Wright, one of the pioneers in this work, who states that for such skilled service as that demanded for vaccine therapy,—"is required a man who has spent years of study to master the technic; to know how to make the vaccines; to know where to look for the microbes; to know how to isolate them; and, most of all, a man with sufficient experience and ability to apply all these things."

DISCUSSION BY DR. JOSEPH HEAD.

Vaccine treatment is only successful when all the depots of infection of the body have been first eliminated by careful diagnosis and judicious treatment. This is particularly the case with pyorrhea alveolaris which I have treated with autogenous vaccines in over seventy cases. Judicious co-operation with the family doctor should be established. All local depots of infection in the mouth should be removed by surgical means in order that the antibodies formed in the blood by the vaccine should have full opportunity to come in contact with the areas of infected tissue. If this is not done and the bacterial masses are left around the teeth and in the gums the antibodies can only attack the exterior portions of this bacterial mass and failures will inevitably result from the vaccine treatment.

I have found in my bacterial examinations of pyorrhea-pockets that there are six principal germs, viz., staphylococcus, streptococcus pyogenes, streptococcus viridans, micrococcus catarrhalis, bacillus influenza, pneumococcus and diphtheroids. In the cases just mentioned these predominate in over 95%, there being an occasional scattering of tetragenus, Friedlander's bacillus and an occasional unrecognizable germ. The reason that my results have been so consistent is probably due to the fact that the technique used for obtaining the material for the autogenous vaccine is such as to exclude the extraneous flora of the mouth.

This technique is as follows: A thin platinum spear of 1/3000 of an inch in thickness is used for obtaining the material for the vaccine. The external portion of the pocket is cauterized with a cautery, then the thin platinum spear heated to a cherry red is plunged to the bottom of the pocket. When this is withdrawn the material contained thereon is supposed to come from the deep walls of the pocket where the controlling infection is supposed to reside. The spear, on being removed, is streaked across the blood agar and sent to the laboratory the same day, where the bacteria are carefully segregated and mixed, according to their species, in the sterile salt solution. Streptococci, micrococci catarrhalis, pneumococci

and bacilli influenza are made up 50 million to the cc. and staphylococci made up 300 million to the cc.

The dosage is a very important factor in this treatment. We should remember in giving vaccines that we are dealing with a substance as vital for good or evil as strychnine or belladonna. Vaccines are not simple remedies as Vaughan's investigations have so beautifully shown. It is my habit to start with a dose containing about five million streptococci and thirty million staphylococci. This is increased steadily week by week until either the full cubic centimeter is given or the patient shows signs of reaction which is made evident by nausea, congestion of the forehead, faintness, purging of the bowels or sharp neuralgic or gouty pains. When these are developed and last for over twenty-four hours, it is always a sign that the dose should be stopped temporarily for a week and then given in very much reduced quantities,—one-half at least. This should be slowly and cautiously raised again, and if possible, kept within the amount that will reproduce the reaction, as it has been my experience that small doses give better results than large. We should always be on the lookout for reaction in giving our doses. Sometimes five or six doses of the same size can be readily accepted and the seventh dose will give a sharp severe reaction. This, according to Vaughan, would indicate that the digestion of the vaccine in the blood has not been complete, and the protein poison is being developed faster than the body can eliminate it.

In closing, I would say that the vaccine treatment is of unquestioned value and in obstinate cases should always be given a fair trial.

A WORD ABOUT PACKAGES AND LABELS.

People are very exacting as to what comes from a drug store; not only must the goods be of the best quality, but the packages in which they are put up must appeal to the sense of neatness. The dry-goods clerk, the shoe clerk, the grocer —in fact, salesmen in all other trades—do not care much about the appearance of the packages they send out. A sheet of paper twisted or rolled around the article, a piece of string, and the thing is done; and nothing better is expected. But with the druggist it is different. We wonder how many druggists appreciate the effect of a neatly-tied package or a simple, neatly-printed label, upon their customers. And yet we know of people who prefer a certain store to another for no other reason than that the goods sent out of it are neater than those coming from the other. What is true of parcel wrappings also holds for labels. A great deal of improvement is noticeable in this respect within the last twenty years. We remember the fantastic labels sported in many drug stores at the time the Japanese art craze swept this nation. Label makers swam with the stream, and some of their efforts were gorgeous beyond belief—so gorgeous that the lettering on the labels was completely lost in the maze of decorative detail. Labels of this kind are seldom seen nowadays, but they turn up once in a while in some obscure village. The intelligent public would not tolerate such things nowadays.

Have your packages neat and your labels plain.—*National Druggist.*