INMUNITY AND CURE IN THE INFECTIOUS DISEASES.

BY VICTOR U. VAUGHAN.

Immunity may be natural or acquired. Natural immunity may be peculiar to the species or race, or to the individual. An example of natural immunity is that of the domestic fowl to anthrax. This animal, even at the time of coming from the shell, is immune to even the most virulent cultures of the bacillus anthracis. It is true that the chick may be made susceptible to anthrax, but this is an artificially induced susceptibility. Immunity is natural to this bird at every period of its life.

The natural inmunity which is peculiar to the individual usually comes with adult life. The young are susceptible to a given disease, but adults of the same species lost this susceptibility and become immune. The young rat is susceptible to anthrax, while the adult is naturally immune, but can be rendered susceptible by exhaustive exercise. The child is highly susceptible to scarlet fever and diphtheria, while the adult, though not wholly immune to these diseases, loses very much in susceptibility and is likely to become affected only when greatly reduced in vitality, or after prolonged and aggravated exposure to poison. Ths evolution of the condition of immunity in these cases is due to the natural development of the functional activity of certain cells of the body. A child and an adult are exposed to the bacillus of diphtheria from the same source. The former becomes affected, the latter does not. The germ is the same, but in the development that converts the child into the adult, the resistence with which the germ must contend has been strengthened. Artificial immunity may be induced by either of the following methods :

1. By an attack of the disease ending in recovery. Until the discovery of Jenner, this was the only known cause of immunity, and even at present it is supposed to be, as far as man is concerned, the most potent cause. It is true, I believe, that the more grave and virulent the disease may be, the greater and more persistent is the immunity that follows. I mention this in order to call attention to the fact that there is a quantitive relation between cause and effect in the production of immunity. In this method of inducing immunity, the substance of the germ itself is introduced into the body. This method found a practical application in inoculstion for the prevention of small pox.

2. By vaccination with a modified and less virulent form of the infection, or by the introduction of at first a very small number of the virulent germs and successive inoculations with larger numbers. The successful inoculations against chicken cholera and anthrax made by Pasteur consist in vaccination with a modified germ, and the valuable investigations of Emmerich and his students in immunizing certain animals to swine erysipelas have demonstrated the results that may be obtained by employing the virulent germ, first in small numbers, and then gradually increasing the doses. Again, it may be observed that the germs themselves are introduced into the body, and again it is also true that the more potent the cause, the greater and more persistent the effect.

3. By one or more treatments with sterilized cultures of the germs. Inmunity against the gems of typhoid fever, cholera, diptheria, tetanus, hog cholera, and several other diseases, has been secured by one or more treatments witn sterilized cultures of these germs. In answering the question, which eonstituent of sterilized cultures gives inmunity, we must bear in mind the following facts.

a. Marked artificial inmunity to the infectious diseases has not been obtained except by the introduction into the animal of the gem substance, either enclosed in the cell wall or in solution.

b. Sterilized cultures contain the germ substance in one or both of these forms.

c. The same immunizing substance exists in the bodies of bacteria grown on solid media and killed by the action of choloroform.

d. The same immunizing effects, varying, however, in degree, are obtained with the bodies of dead bacteria morphologically intact or in solution, with living bacteria modified and reduced in virulence, and with very small numbers of the virulent germ.

With these demonstrated facts before us, I am ready to believe that the immunizing substauce is a constituent of tne bacterial cell itself, and as each kind of germ has its own peculiar poison (which in small doses confers immunity), this poison cannot come from the cell wall; nor is it really a split product of tne germ's action, but it is the essentially characteristic part of the cell--that part wnicn gives to tne germ its distinctive properties. I believe that it is the nuclein.

The three methods of inducing immunity which we have mentioned reduce themselves to one and the same principle, i. e. the introduction of germ nuclein into the body.

The immunity that results from an attack of the disease is caused by the introduction of germs living and more or less virulent. That which comes from vaccination is due to the introduction of germs living but modified and reduced in virulence, or administered in small quanity; that which is obtained by one or more treatments with sterilized cultures is secured by the introduction of germ nuclein so modified that it is no longer capable of reproducing itself.

4. By treating a susceptible animal with the blood serum of an immune animal.

Strange as it may seem, the principle upon which immunity is secured when the blood serum of an immunized animal is injected into a susceptible one is essentially the same as that which holds good in the methods already discussed. A horse is rendered inmune to tetanus by previous treatment with the modified bacterial proteid of that disease. As a result of these treatments, a tetanus antitoxin is generated in some organ or organs of the horse and circulates in its blood. When the blood clots, this antitoxin is found in the serum, and if the s serum be injected into a mouse in sufficient quanity, this animal becomes for the time being immune to the tetanus poison, provided that the poison is not introduced in quantities so large that it will not be destroyed by the antitoxin that has been brought over from the horse. The immunity actnally does nor belong to the mouse, it still belongs to the horse. It is stolen property and will soon be lost. The cells of the horse and not those of the mouse make the antitoxin. The mouse for the time being becomes physiologically a part of the horse, and it is by virtue of this relationship that the former is for the time being immune to tetanus.

We have seen that in all cases the cause that brings into existance the condition of immunity is a bacterial proteid. Nnw, in order that this inciting cause may induce the condition of immunity, it must act upon something. Upon what organs of the body does it act? We have many reasons for believing that the organs acted upon are, the spleen. bone narrow, thyroid and thymus glands, and possibly other grandular organs. Tizzoni and Cattani have found that rabbits from which the spleen has been removed cannot be immunized to tetanus. Supposing that the above mentioned organs are concerned in the production of immunity, in what way do they act? Do they

elaborate antitoxins, and if so, what can be said about the natnre of these antitoxins? These are questions in which I have been deeply interested for some time, and which I have attempted to solve. In this attempt, I have born in mind the fact that these organs are the source of the nucleated white blood corpuscles. Do these corpuscles contain a germicidal or antitoxie substance, and if so, what is its nature? The chief chemical constituent of nuclei is a substance called nuclein, some of the general properties of which are known to physiological chemists. Can it be that nuclein is the germicidal or antitoxic substance? Have the nucleins in general or as a class any germicidal action? As methods of insolating the nuclein are known, these questions can be answered by experimentation, and this I have attempted to do.

At first I tried to prepare an active nuclein from compressed yeast, but the results were not satisfactory. Compressed yeast contains a large amount of water and starch. The large proportion of the first mentioned constituent caused a very small yield of nuclein, and there were many dfficulties in the complete separation of the starch. There were, however two other and more serious objections to the use of compressed yeast. The first of these is due to the fact that such yeast contains bacteria to begin with, and the nuclein contained in this yeast has already been decomposed. The second difficulty lies in the fact that compressed yeast contains many dead cells, and an active nuclein can be obtained only from living, healthy cells.

From the cells obtained from pure cultures of yeast, I have obtained an active nuclem by the following method:

The cells from pure cultures of yeast are washed with sterilized water, then treated with a five per cent solution of potassium hydrate and filtered through paper. Sterilization of the paper is not necessary. The filtrate is feebly acidified with hydrochloric acid and the proteid precipitated with 96 per cent alcohol. The precipitate is washed with alcohol by decantation until the supernatant fluid remains colorless. The precipitate is then collected upon a filter, and after all the alcohol has passed through, it is dissolved in very dilute potassium hydrate (.25 to .50 per cent). This inquire nuelein hus marked germicidal effects upon the staphylococcus pyogenes aureus, albus, the anthrax bacillus, and the germs of typhoid fever, Asiatic cholera, and tuberculosis.

The following experiment will illustrate the action of this nnclein upon the bccillus of tuberculosis: A loop of tuberculous sputum, showing from 40 to 60 bacilli in each field when stained, was stirred up in beef tea, allowed to stand for twenty-four hours at 38° C. and injected into the abdominal cavity of guinea pig No. 1. Another loop of the same sputum was added to a solution of 30 milligrams of inpure yeast nuclein in .08 per cent of potassium hydrate, and this was allowed to stand in the incubator at 38 degrees C for twenty-four hours, and then injected into the abdominal cavity of guinea pig No. 2.

At the expiration of fourteen days, both of those animals were killed. The omentum of No. 1 was a tuberculous mass throughout, while No. 2 showed not the slightest evidence of the disease.

I have prepared testicular nuclein from the testicles of of the bull, dog. guinea pig, and rat. The testicles are stripped of their investing membranes as soon as removed, rubbed up and extracted repeatedly with a mixture of equal volumes of absolute alcohol and ether. Then, the testicular snbstance is digested for some days (until the supernatant fluid fails to respond to the biuret test for peptones) at 40 degrees C. with pepsin and .2 per cent hydrocoloric acid. The undijested portion which contains the nuclei is collected on a filter paper and washed, first with .2 per cent hydrochloric acid, then with alcohol. Finally it is dissolved in a .5 per cent solution of potassium hydrate and filtered through a Chamberland filter without pressure This solution is clear, more or less yellow, and feebly alkaline. On the addition of nitric acid, a white precipitate forms and dissolves colorless in the cold on the further addition of nitric acid. This nuclein does not give the biuret reaction, but does respond to the Millon test. The nitric acid solution of the precipitate becomes yellow on the addition of ammonia. This nuclein also has germicidal properties, as is demonstrated by the following experiment:

A solution of testicular nuclein of unknown strength, obtained from the testicles of a bull, was diluted with four volumes of physiologic salt solution, inoculated with the bacillus anthracis, and plates made with the following results;

Time,	Immediate.	30 min.	1 hr.	2 hrs.	3 hrs.
Number of colonies,	730	6	0	0	0

Other nucleins with germicidal properties have been obtained from the thyroid gland, spleen, and from the yolks of eggs.

These experiments render it highly probable that the nuclein-forming organs of the body have some concern in the production of immunity. The nucleins formed by these cells or in these organs pass into the blood partly in the form of multinuclear white corpuscles—the so-called phagocytes.

In order to state my views upon immunity in a condensed form I will summarize as follows: There must be three factors in the production of immunity in an animal naturally susceptible: First, there must be an inciting or immunizing substance introduced into the body. This substance is the nuclein of the germ. These nucleins, when introduced into the bodies of certain animals, in certain amounts and under certain conditions, have the property of so stimulating the activity of certain organs that those organs produce and supply to the blood an antidote to the substance introduced.

Secondly. The organs whose activity is stimulated by these immunizing agents are those such as the spleen, thyroid gland and bone marrow, which manufacture nucleins.

Thirdly. The antidotal substance is a nuclein. The kind and amount of nuclein formed will depend upon the nature of the inciting agent and the condition of the organ or organs acted upon.

I use the word "nuclein" in a broad sense, including the true nucleins, nucleinic acid, and nucleo-albumins. By the term "nuclein" I mean that part of the cell which under normal conditions is endowed with the capability of growth and reproduction, which assimilates other proteids and endows these assimilated substances with its own properties. It is that part of the cell which gives in its individuality. Whether these nucleins while in solution and devoid of morphologic unity are still capable of assimilating allied bodies cannot at present be satisfactorily determined.

We can suppose that the process of immunizing an animal proceeds in something like the following manner:

The modified virus of tetanus is introduced into some distant part. In some unknown way, the spleen is stimulated to action and secretes a nuclein which is carried partlp in solution, partly in the form of multinuclear cells, to the invaded party of the body, and the tetanus poison is converted into the nuclein coming in contact with it, or is otherwise rendered inert. Later, a larger quantity of the tetanus poison is introduced, and now the acspleen ts more promptly and energetically than before. This promptness and energy of action are increased by exercise, and finally an amount of tetanus culture of full virulence, suf-

ficient to kill an animal whose spleen has not been subjected to this training, may ba introduced without ill effect.

On this theory, the production of immunity consists of a special education of certain cells and artificial immunity becomes essentially cellular. The differance between immunity and tolerance I conceive to be this: In the former, the of certain organs become aggressive, a special function is developed. The poison introduced is destroyed. In tolerance, there is no aggressive action on the part of any organ.

There is no development of speeial functions. The poison introduced is not destroyed, it only fails to kill.

Now what can be said about the relation between thc principles of inmunity and those of cure? Are they thə same? I think that there are essential differences. In the first place, the substances with which inmunity is induced are not applicable in the production of a cure. They are already in the body and have failed to stimulate the nuclein-forming cells in such a manner as to cause their own destruction. To introduce more of the bacterial poison after the invading virus has established itself in the system will only strengthen the invader.

If I am right concerning this differance between the agents of inmunity and cure, to what source shall we look for curative substances in the infectious diseases? Either we must introduce into the body some germicide formed by other cells, or we must employ other agencies for the purpose of stimulating the nuclein forming cells.

Blood-serum therapy offers the first of these alternatives, and now that we know that the germicidal constituent of the blood is a nuclein, blood-serum therapy will give place to nuclein therapy, and with the latter there is more hope of accomplishing good results because it reduces the size of the dose.

Now that we have learned that the animal body itself generates a germicide more powerful in its action than corrosive sublimate, and since we know how to increase the amount of this substance in the blood and can insolate it and inject it into other animals, a new theory of the treatment of diseases is opened to us.

If it be possible to kill the germs or destroy thc bacterial poison after the development of an infectious disease, by the introduction of a germicde or a toxicide formed by other cells than those of the infected person, then we may expect that cures for diseases of this kind will be found in the near future. Experimentation offers the only means of ascertaining whether or not this be possible. The recently reported cases of tetanus successfully treated with the antitoxin of Tizzoni and Cattani, obtained from the blood of animals which have been rendered immune to this disease, are in accord with this principle.

If nuclein therapy fails us, we must strive to find agents that will stimulate the nuclein forming glands. This probably is the shief factor in the climatic treatment of tuberculosis, but so far as our knowledge of medicinal substances that will accomplish this result goes, we are practically and wholly ignorant.

I have used the "cure," limiting its meaning to the destruction of the germ or other poison. If we could destroy all of the bacilli in the body of a tuberculous patient, would a cure be effected? If we ever reach this desideratum. nature will probably do the rest.

CONSCIOUSNESS UNDER THE INFLUENCE OF CANNABIS INDICA.

BY E. W. SCRIPTURE, YALE UNIVERSITY, NEW HAVEN, CONN.

THE statement is generally madc that the extract of *Cannabis Indica* (flowers of the Indian hemp whose leaves and resin furnish hashish) causes time and space to be greatly lengthened in consciousness. Wishing to know what is meant by these statements I obtained the prescription:

Rx.
Ex. Cannabis Indicæ (P. D. & Co.) 1 oz.
Alcohol 20 oz.
M. Lig. Alcoholic solution of extract of Cannibis indica. One drachm contains three grains. Commencing dose ten drops containing one-quarter grain of the extract.

One evening I took ten drops as prescribed. No effects were noticed for over 45 minutes. Concluding that the dose was not strong enough I gave up the experiment for that occasion and drank a mug of beer preparatory to retiring. The narcotic action of the hops probably assisted in bringing on the effects of the dose. It is to be noted that my consciousness is very suspectible to the influence of narcotics.

For over an hour and a half, till final sleep occurred, and in a lesser degree throughout the next day, several important changes in mental life were observed. The most striking was the fluctuation of attention. The experiments of Lange (Philos. Studien, IV, 390) and of Eckener, Pace and Marbe (Philos. Stud., VIII, 343, 388, 615) have demonstrated the phenomenon as a normal condition for weak stimuli. For example, the faint ticking of a watch is alternately lost and heard. It holds good also of stronger sensations; the ticking of a clock, although loud, will vary in its apparent intensity. The immense fluctuations under the influence of hemp can be illustrated by the following case which occurred several times. A horse car is heard approaching; shortly afterward I find that the sound enters anew into consciousness; again it enters anew, and this is repeated through all the phases of approach, passage and retreat of the car. While listening to the sound, it somehow slips away, just as in Lange's experiment, and returns after a while. In describing the phenomenon I have avoided saying that the sound is heard, dies away, is heard again; all that is known in consciousness is the repeated entrance of the sound and the memory of the fact that it had been lost out of view a moment before.

The next most striking phenomenon was the remoteness of objects in their relation to myself. After the phenomenon had begun to be noticeable I wrote down on the spot the condition I found myself in. The words are: "Events seem more distant in feeling of subjectivity—events happened seem to have happened in time remotely related to the observer—apparently the time seems quite remote—yet after all it is not really longer than the usual time. Events in space are less personal, yet not further away. My feet on a chcir in front do not seem so close to me but my legs are not longer." I could estimate a period of five minutes quite correctly; I could touch objects without any noticeable error of estimation. Yet events of five minutes ago belonged to the past and objects on the table beside me seemed scarcely to be there for me to reach them. During the following day I several times noticed that a minute after seeing a place or an object, the event might as well have occurred on the previous day.

All these phenomena, in a minor degree, I have frequently observed when depressed by dull weather or by fatigue. On those occasions and under the influence of hemp there seems to be a partial loss of power of volition in general. This, I think, gives the key note to the phenomena noticed. Holding a sensation steadily under attention requires an effort, in fact, even when the sensation is strictly attended to, it unquestionably undergoes continual fluctuation of conscious intensity. Attention, even in its simplest form, the so-called involuntary attention,