any lasting agricultural prosperity. The demands on agriculture increase with each passing year, and science will show the way to make surely productive those areas which are now of little value because of deficient rainfall. Water is the chemical reagent which is most potent in crop production. The chemist and the physicist, with the help of the engineer, will show the way to its most economical utilization. Chemistry will supply the mineral foods which the plant needs. In the early history of a new country we uniformly notice the rapid decrease in the fertility of the virgin soil. This is due to a system of farming little better than robbery. Its basic principle is to take from the soil everything possible and give nothing in return. Necessity finally puts an end to such practices and education provides the means for the inauguration of scientific agriculture. Then the exhausted fertility of the soil begins to return. The fields become more productive and each step in advance is retained and becomes the base for further progress. We may confidently predict that the future years will see abundant food for the increasing millions of population. Life will have less of labor and more of leisure for study and recreation. In all the arts which will help in the amelioration of the conditions of existence, chemistry will enter as an important part.

The state builds well, therefore, in an endowment of the kind we celebrate today. As in astronomy we study the infinitely great, so in chemistry we investigate the infinitely small. We seek the very nature and origin of matter and thus come near to those first combinations of simple cells which condition the vital spark.

In the early history of the race we find men dedicating fountains, groves and temples to the worship of mythical deities. To-day we set apart churches, schools, libraries and laboratories for the public good.

More than a liberal training, more than professional ability and technical skill, are those attributes of the man, which make him a source of help to the family, the community, the municipality and the state. Providence in the family, morality in the community, public spirit in the municipality and patriotism in the state are the real purposes of all training. To these ends the educated man must be a bread-winner, of upright conduct, ready to give his services to the city and his life to the republic. He must know how to produce wealth. He must be acquainted with the needs of the community. He must understand the service he is to render to the municipality and have that enlightened patriotism which, while not separating him from a political party, acts first of all for the good of the whole people. The future years will find the leaders of the people among the graduates of the universities, because if the universities are not remiss in their duties, their graduates will be better fitted for leadership. There is no talisman in a diploma. Only ability will count. We recognize the important contributions which all branches of learning will make to this equipment of the successful man of the coming years. In dedicating this building to chemical science it has seemed only meet to point out some of the ways in which our science may aid in the work.

H. W. Wiley.

U. S. Department of Agriculture.

THE HUXLEY LECTURE ON RECENT STUDIES OF IMMUNITY WITH SPECIAL REFERENCE TO THEIR BEARING ON PATHOLOGY.

II.

The methods hitherto employed for the study of bacterial poisons have not generally been calculated to reveal the presence of toxins with the characters indicated, even if such existed in the cultures. Recently, however, a beginning has been made in this direction, and we have already become acquainted with certain toxins of an interesting nature, to which I desire to direct your attention.

Intrinsically and in their general bearing upon the subject before us, the recent investigations of Flexner and Noguchi upon the constitution of the toxins in snake venom are of special importance. It was in snake venom that Weir Mitchell and Reichert first demonstrated the existence of that class of poisons often called, although with doubtful propriety, toxic albumins. Investigations of snake toxins are of peculiar interest for many reasons, not the least of which is their resemblance to bacterial toxins. The demonstration by Sewall of the possibility of active immunization from venom, and the further studies by Calmette and by Fraser of this phenomenon, and especially of the protective and curative properties of antivenin are well known.

Until recently it has been generally held that the venom toxins resemble in molecular structure the diphtheria and the tetanus toxins in being single bodies with a combining or haptophore group and a toxophore group of atoms. The researches of Flexner and Noguchi, now in progress, of which only the first part has been published,* necessitate a quite different conception of the nature and manner of action of venom toxins from that previously entertained. I have followed with great interest the work of Professor Flexner on toxins, begun several years ago in my laboratory when he was my assistant and associate, and since continued along new lines in his laboratory at the University of Pennsylvania, and I wish to acknowledge his generosity in permitting me to use in this lecture certain unpublished results of his and Noguchi's investigations.

These investigations have shown that the toxic action of venom upon red blood corpuscles, leucocytes, nerve cells and other cells is like that of the duplex cytotoxins already described—that is, it depends upon the combination of intermediary bodies contained in the venom, on the one hand with the animal cells for which these bodies respectively have affinities, and on the other hand with corresponding complements contained, not in the venom, but in the cells or fluids of the animal acted on. For example, it is well known that the addition of venoms to fresh blood brings about the quick destruction and solution of the red corpuscles. If, however, certain venoms be added to red corpuscles which have been thoroughly washed with isotonic salt solution so as to remove all the complement, the corpuscles are agglutinated but not dissolved, although it can be shown that substances from the venom (intermediary bodies) have entered into combination with the corpuscles. If now a little fresh serum which contains the complement, and by itself may be an excellent preservative of normal corpuscles, be added to these venomized corpuscles, they are promptly dissolved.

Preston Kyes, working in Professor Ehrlich's laboratory, in an investigation just published* on the mode of action of cobra venom, confirms the conclusion of Flexner and Noguchi concerning the amboceptor nature of cobra venom, and adds

* Flexner and Noguchi, 'Snake Venom in Relation to Hæmolysis, Bacteriolysis and Toxicity,' *Journal of Experimental Medicine*, March 17, 1902, Vol. VI., p. 277.

* Preston Kyes, 'Ueber die Wirkungsweise des Cobragiftes,' *Berl. klin. Woch.*, 1902, Nos. 38 and 39. I am greatly indebted to my fri nd Professor Ehrlich and to my former pupil Dr. Kyes for putting me in possession of the main results of these interesting experiments before the date of their publication.

much that is new and important to our knowledge of this subject. He finds that the washed blood corpuscles of certain animals are directly dissolved by cobra venom, while those of other animal species require the subsequent addition of complements or adjuvants to bring them under the influence of the venom. But even in the former case a complementary body is essential to the reaction, this, however, being not a serum complement, but an endocomplement contained within the red corpuscles. Of great significance is the demonstration by Kyes of still a third substance, namely lecithin, which is capable through combination with the venom intermediary body of completing the hæmolytic potency of venom.* The discovery for the first time of a definite, crystallizable substance with the power of uniting, like a complement, with an intermediary body, and thus completing the formation of a cytotoxin, is evidently of fundamental importance. The suggestion by Ehrlich and Kyes that possibly the cholin group is the toxophore group of lecithin is particularly interesting in the light of F. W. Mott's valuable studies of chemical processes concerned in degenerations of the nervous system.

The researches of Flexner and Noguchi and of Kyes, therefore, have taught us that in poisoning by venom the bodies of human beings and of animals contain in the form of complements, or alexins† as they are also called, the substances which are most directly concerned in the act of poisoning. The venom serves merely to bring into the necessary relation with constituents of the body cells poisons we already harbor or may generate, but which are harmless without the intervention of intermediary bodies. These poisons within us are powerful weapons, which when seized by hostile hands may be turned with deadly effect against our own cells, but which are also our main defence against parasitic invaders. We see here as everywhere that nature is neither kind nor cruel, but simply obedient to law.

Flexner and Noguchi have demonstrated experimentally that, like the hæmolytic, so also the leukotoxic, the neurotoxic, and other cytotoxic properties of venom depend upon combinations of venom intermediary bodies with complements contained in the cells poisoned by venom or in the fluids bathing these cells. Particularly striking are their experiments showing *in vitro* and under the microscope the cytolytic action of cobra venom upon certain large molluscan nerve cells in the fresh state. The complement essential to this reaction is contained within the nerve cells. In previous experiments of Flexner and Noguchi there had been indications that a special class of intracellular complements are concerned in some of the toxic effects of venom upon cells. The positive demonstration by Preston Kyes of a special class of intercellular complements or endocomplements is unquestionably of great pathological interest, and seems destined to play an important part in the explanation of many morbid conditions in connection both with endogenic and with exogenic intoxications, probably also in such phenomena as self-digestion or autolysis.

Snake venom is a rich mine of diverse toxins, and, on account of its pathological importance, I must mention one of the cytotoxins discovered there by Flexner and

* The objections made by Calmette (*Compt. Rend. Acad. des Sc.*, 1902, T. CXXXIV., No. 24) to Flexner and Noguchi's interpretation of their experiments as to the amboceptor nature of venom have been completely overthrown by the experiments of Preston Kyes.

† There is some objection to the use o the term 'alexin' as a synonym for 'complement' as the former was applied originally by Buchner to substances which we now know to be combinations of complements with intermediary bodies.

Noguchi, as it may be that a similar toxin is produced by certain bacteria, and under still other conditions. As is well known, one of the most striking lesions resulting from poisoning by certain venoms is the occurrence of abundant hæmorrhages in various tissues of the body. This effect has been generally attributed to the direct action of venom on the red corpuscles and on the coagulability of the blood, but the experiments of Flexner and Noguchi indicate that these hæmorrhages are due to the presence in venom of a cytotoxin which has the power of dissolving endothelial cells—in other words, an endotheliolysin. Dr. Flexner suggests the name 'hæmorrhagin' for this special toxin which causes extravasations of blood through its direct solvent action upon capillary endothelium, an effect which is readily demonstrated under the microscope. It is hardly necessary for me to stop to emphasize the clinical and pathological importance of the discovery of an endotheliotoxin, a kind of poison which may prove to be of special significance in the interesting group of hæmorrhagic infections, and perhaps also in purpura and kindred affections.

The foregoing newly-discovered facts, which I have sketched only in bare outline, illustrate in a striking way the fruitfulness of methods and conceptions which we owe to recent studies of immunity. The results of these investigations, however, are significant beyond the mere facts disclosed, important as these are. They have for the first time revealed in normal toxic secretions, readily introduced under conditions of nature into the tissues of man and animals, cellular poisons akin to the complex hæmolysins, neurotoxins, and other cytotoxins of immune and some normal serums, which have aroused so much interest and experimental study during the past four years. The most noticeable difference between the venom cytotoxins and those hitherto observed in immune serum is the far greater resistance to heat of the intermediary bodies of the former; but we are already acquainted with considerable variations in the sensitiveness to heat both of different intermediary bodies and of complements. That snake venom should contain only one half of the complete poison, the other and the really destructive half being widely distributed in the blood and cells of man and of animals, is an instance of a curious kind of adaptation, of interest from evolutionary, as well as from other points of view.

In consideration of the often emphasized analogies between venom toxins and bacterial toxins, these facts render it highly desirable to make a systematic search of bacterial cultures by proper methods and under suitable conditions for complex cytotoxins. At present substances of this nature are not known to exist in our cultures. There have been discovered, however, within the past three or four years certain bacterial toxins which have a curious resemblance in some of their properties to the complex antibodies of blood, although, so far as they have been carefully studied, they appear to have the simpler constitution of the soluble toxins, like those of diphtheria and of tetanus. I refer to the bacterial hæmolysins, leucolysins, hæmagglutinins, precipitins and coagulins. There is no reason to suppose that this list exhausts the number of those actually present, for it is evident that it includes chiefly bodies readily demonstrable in test-tube experiments. It would be surprising if cytotoxins which act specifically upon red and white corpuscles were the only ones of this class produced by bacteria; in fact, we have every reason from pathological observations to believe the contrary.

It has become evident that more refined methods than mere observation of the coarse effects of injecting into animals the filtrates or the killed bacteria of our cultures are required for the detection of the subtler and more specific cellular poisons. Instances are rapidly increasing in which by improved methods cultures of bacterial species once believed to be practically devoid of toxicity are found after all not to be so poor in toxins, even of the soluble variety. One of the earliest and most instructive illustrations of this is the discovery by Van De Velde of a leucocyte-destroying poison, named leucocidin, in exudates caused by infection with *Staphylococcus aureus,* and also in filtrates of staphylococcus cultures, which had been previously regarded as almost entirely free of toxic power.

More widely distributed in cultures of different species of bacteria are the hæmolysins, of which the first example, discovered in 1898 by Ehrlich in cultures of the tetanus bacillus, was carefully studied by Madsen the following year, and which have since been investigated by Kraus with Clairmont and with Ludwig, Bulloch and Hunter, Neisser and Wechsberg, Todd, Besredka and others. The list of bacterial species known to produce in cultures substances of this nature capable of dissolving red blood corpuscles is already a long one, and includes the bacilli of tetanus, of green pus, of typhoid fever, of acute dysentery, of diphtheria, of plague, the pyogenic staphylococci and streptococci, the pneumococcus, and many other bacteria. Nuttall and I noted in our first descriptions of *Bacillus aerogenes capsulatus* over ten years ago its capacity of laking blood, so that I was not surprised to find recently that a hæmolysin can be demonstrated in cultures of this organism. The blood-destroying property appears to stand in no definite relation to virulence, nor is it limited to pathogenic bacteria. It pertains also to many putrefactive bacteria. The strongest bacterial hæmolysin hitherto observed was found by Todd in cultures of *Bacillus megatherium,* which is a widely distributed saprophyte.

As already stated, none of these bodies has been shown to belong to the class of complex hæmolysins in blood, which have been far more exhaustively investigated than any other of the specific antibodies. Doubtless there is at present among bacteriologists too great a tendency to attribute to the less carefully studied antibodies characters which have been worked out in detail only for the hæmolysins of immune serum. It would lead too far to attempt here a discussion of the special characters of the various bacterial hæmolysins, which present in different specimens curious and at present unexplained divergences as regards resistance to heat and several other properties. It must suffice to indicate briefly what is known of the pathological importance of this interesting group of bacterial toxins.

In view of the abundant clinical and pathological evidence of extensive destruction of red corpuscles in the course of many infectious diseases, it is certainly significant to find that many bacteria are endowed with a specific hæmolytic power. The question is how far we are justified in applying to the actual conditions of infection the existing experimental data upon this subject. Assuredly here, as everywhere, results of test-tube experiments, helpful in suggestion as they may be, should not be utilized without further evidence to explain morbid phenomena within the infected human or animal body. While much more work upon this subject is needed before our information will be exact or complete, the observations and experiments of Besredka,* Kraus and Ludwig,† and

* Besredka, *Annales de l' Institut Pasteur,* 1901, XV., p. 880.

† Kraus and Ludwig, *Wien. klin. Woch.,* 1902, p. 382.

others have already demonstrated that bacteria may exert their blood-destroying power within the living body. This hæmolytic capacity of microorganisms affords an explanation, although certainly not the only one, of the secondary anæmias which are such a marked feature of many infectious diseases, as streptococcic and other septicæmias, pneumonia, typhoid fever, scarlatina, and others. The hæmoglobinuria which is a recognized although rare complication of various infectious diseases may be referable to intoxication with unusually powerful bacterial hæmolysins, or to an exceptional lack of resistance of red corpuscles.

Hæmoglobin, however, is not necessarily present in solution in the blood plasma, for the destruction of the damaged red corpuscles may take place within the large phagocytes of the spleen and the hæmolymph glands, as is well known to occur on an extensive scale in typhoid fever and some other infections. A familiar example of the action of bacterial hæmolysins is the post-mortem reddening of the inner lining of the heart and blood vessels, an effect which may be due to putrefactive bacteria or may appear very soon after death, especially from septicæmia caused by *Streptococcus pyogenes*, which, as has been shown, may lake the blood during life.

The fact that certain common saprophytic bacteria may produce energetic hæmolysins, as pointed out by Kraus and Clairmont and by Todd, has a possible bearing upon the etiology of certain obscure anæmias not of infectious origin, particularly upon the interesting observations and the theory of William Hunter concerning their causation by absorption of toxins from the alimentary tract. Todd found cultures of *Bacillus megatherium* so strongly hæmolytic that the intravenous injection of 1 c.c. of the filtrate into guinea-pigs was followed by hæmoglobinuria, 10 c.c. being fatal. Human red corpuscles are sensitive to this hæmolysin.

Normal human and other blood serums contain in varying amounts antihæmolysins, which protect the red corpuscles from the action of some of the bacterial hæmolytic agents. Specific antihæmolysins are readily produced by immunizing injections of bacterial hæmolysins, and are generated also in the course of infections. Lang suggests that the augmentation of the osmotic resistance of the erythrocytes which has been noted in some infectious diseases, as well as in icterus and some other morbid conditions, may be a reactive phenomenon caused by the presence of hæmolytic toxins.

Intimately associated with the hæmolysins in cultures are the bacterial hæmagglutinins,* substances which have the power to clump red blood corpuscles. Among unicellular organisms both the capacity to produce agglutinins and the aptitude for agglutination seem to be very widely distributed. The bacterial hæmagglutinins, in analogy with the bacterial hæmolysins, are apparently of simpler constitution than the serum agglutinins, being destroyed at 58° C., whereas the latter are not injured by temperatures under 70° C. In order to demonstrate in cultures the hæmagglutinins it is generally necessary to eliminate in some way the action of the associated hæmolysins, which can be done by using small quantities of the culture fluid or by keeping the mixture of fluid and red corpuscles at zero temperature.

I know of no observation directly demonstrative of the action of bacterial hæmagglutinins within the living body in infections, but this subject is of such recent knowledge that it has been as yet scarcely investigated. Certainly there are morbid conditions which seem highly indicative of

* Kraus and Ludwig, *Wien. klin. Woch.*, 1902, p. 120.

the operation of substances agglutinative of red corpuscles. Probably every one with large experience in the examination of fresh blood in disease has noticed that sometimes red corpuscles, examined immediately after withdrawal of the blood, have a peculiar tendency to form clumps which cannot readily be broken up. This phenomenon, which is certainly suggestive of the action of an agglutinating agent, I have observed especially in some cases of septic infections and of cirrhosis of the liver.

Furthermore, I would emphasize the support given by the recognition of hæmagglutinins to views advocated many years ago by Hueter and by Klebs concerning the occurrence of thrombi composed of coalesced red blood corpuscles. Such thrombi I believe to be not uncommon in typhoid fever and other infections, especially in small blood vessels. I have elsewhere called attention to the evidence in favor of the interpretation of many of the hyaline thrombi as derived from agglutinated red corpuscles.

It can scarcely be doubted that substances agglutinative of white blood corpuscles are also produced by certain bacteria, and that these are concerned in the clumping of pus cells and of leucocytes within the living body, but it would not be profitable to discuss this matter without more exact information than we now possess.

In this connection I may say that not only the discovery of the bacterial hæmagglutinins, but also that of the hæmolysins and the leucolysins, is likely to shed new light upon certain aspects of the difficult subject of thrombosis. The red corpuscles undergo various morphological changes under the influence of different bacterial hæmolysins acting with varying intensity. Distortions of shape, throwing out of projections, and detachment of colorless particles resembling platelets, can sometimes be seen. These observations are of special interest with reference to the doctrine, already strongly supported, that platelet thrombi originate from disintegrated red corpuscles. Levaditi, and Neisser and Wechsberg, have described, as the result of intravenous injections of *Staphylococcus aureus*, areas of coagulative necrosis in the rabbit's kidney, which they attribute to thrombi composed of disintegrated leucocytes caused by the staphylococcus leucocidin, to which I have already referred.

I have dwelt at some length, although of necessity incompletely, upon the bacterial hæmolysins, leucocidins and hæmagglutinins, because we are better informed about these agents than concerning other members of this recently recognized class of bacterial toxins. I have already expressed the opinion that similar poisons acting specifically upon other cells of the body are produced by bacteria; indeed neurotoxins and nephrotoxins of this type have been reported. The difficulties in the way of direct proof of the existence of these other bacterial cytotoxins are greater than in the case of those acting upon the red and the white blood corpuscles, but doubtless they can be overcome. Of course we have evidence of the action of bacterial poisons upon various body cells, but this is not enough. At present we can apply only in a vague and unsatisfactory way to the explanation of pathological processes most of the knowledge of this kind which we possess. What is urgently needed is a separation of these poisons and a determination of their source, constitution, mode of action and degree of specificity along such lines as have been followed so fruitfully in the investigation of the soluble diphtheria and tetanus toxins, those other toxins of bacteria and of venom already considered, and the cytotoxins of normal and of immune serum. The path leading apparently in the right direction has already been opened, and, if I mistake not, its further pursuit is most promising of valuable results in the near future.

Consider by way of illustration how helpless we now are in our efforts to explain the characteristic lesions of typhoid fever on the basis of our knowledge of the properties of the typhoid bacillus. That these lesions are referable to the action of toxins cannot, I think, be seriously questioned. Especially from the investigations of Mallory, we know that the most characteristic histological changes of this disease consist in the proliferation of the reticular or so-called endothelial cells of the lymphatic tissue of the intestine and the mesenteric glands and of similar cells in the splenic pulp, and in the assumption by these proliferated cells of remarkable phagocytic activities towards the lymphocytes in the former situations and towards the red corpuscles in the spleen. Mallory believes that these changes are best interpreted by supposing that the typhoid toxin directly stimulates to proliferation the endothelial cells, which then devour their offspring, the lymphocytes, and the red corpuscles.

I have suggested as another explanation that the typhoid bacillus produces a lymphocytotoxin and a hæmolysin, and that the proliferation of the fixed cells is partly compensatory and partly for the increased production of macrophages. We already know that this bacillus generates a hæmolytic agent, and we also know that one of the effects of injection of hæmolysins is to increase greatly the number of macrophages containing red corpuscles in the spleen.

Through the kindness of Professor Flexner I have had the opportunity of studying the extraordinary changes produced in all the lymphatic glands and in the bone marrow of rabbits by injections of lymphotoxic or myelotoxic serum obtained by treating a goose with lymphatic or marrow tissue of the rabbit. One of the most striking effects of this poison for lymphocytes and other leucocytes is the very extensive proliferation of the reticulum cells in the lymphatic nodes and of the marrow cells. In the light of these observations it is clear that a positive demonstration of the production of a lymphotoxin by the typhoid bacillus would materially advance our understanding of the morbid anatomy of typhoid fever. Another lesion of this disease, only second in importance to those mentioned, is the occurrence of plugging of the small vessels. Dr. Fisher, in my laboratory, has recently shown that such thromboses are produced by the experimental inoculation of rabbits with the typhoid bacillus. I have already pointed out that many of these plugs are agglutinative thrombi.

Of course infectious diseases other than typhoid fever could also be cited, did time permit, as equally forcible illustrations of the aid which pathology may reasonably expect from more precise knowledge of the bacterial cellular poisons. It is probable that such knowledge will lead to improvements in the quality for therapeutical purposes of the so-called bacteriolytic serums, some of which, as now prepared, are not so wholly devoid of antitoxic properties as is often represented. We may also anticipate from investigations of the character indicated much light upon one of the most puzzling of bacteriological problems—the localization of bacteria in disease. Toxic lesions and the plugging of small blood vessels are certainly often of decisive influence in determining this localization, as has been demonstrated especially for the staphylococcus pyæmias by Muscatello and Ottaviano.*

* Muscatello and Ottaviano, *Virchow's Archiv*, 1901, CLXVI., p. 212.

The toxins to which I have chiefly directed your attention in this lecture are those produced by bacteria. But, as already pointed out, we now know that the animal body has the power to produce specific poisons directed not only against invading bacterial cells, but also against all sorts of foreign cells. Following the discovery by Belfanti and Carbone in 1898 of this capacity in relation to injections of blood a wholly new domain of biology has been opened to experimental research. Attention has been withdrawn for the moment to a considerable extent from the bacterial toxins and concentrated upon the animal cytotoxins. Here new facts and conceptions of absorbing interest have been disclosed in an abundance and with a rapidity which are simply bewildering.

It was my original design to include in this lecture a consideration in some detail of these animal cytotoxins, but so much time has been occupied with other aspects of the subject that I am compelled to abandon this intention. This is perhaps less to be regretted, inasmuch as I understand the main purpose of these lectures to be the presentation of applications to medicine and surgery of scientific discovery, and it is precisely this side of the recent work on animal cytotoxins which seems to me in the main not yet ripe for profitable discussion on this occasion. It is true that facts of much scientific and practical interest have been discovered by the investigations, initiated by Shattock and by Grünbaum, followed by Landsteiner, Ascoli, Eisenberg, Kraus and Ludwig and others concerning the isoagglutinative and isolytic properties of human serums in health and in disease.

But the really great practical questions in this domain relate to the production of autocytotoxins in the human and the animal body. What is the nature of that very efficient regulatory mechanism underlying the horror autotoxicus (Ehrlich) which prevents either the action or the formation of autocytotoxins in consequence of absorption of our own degenerated and dead cells? Can this protective mechanism be overthrown by pathological states and self-generated cellular poisons become operative in the causation of anæmias, hæmoglobinurias, chronic interstitial inflammations, uræmia, eclampsia, epilepsy and other diseases? To these and similar important questions the existing experimental data seem to me too insufficient and inconclusive to furnish any decisive answer at present. I share, however, the hope and belief of many that here is a field for exploration which, although surrounded with many difficulties, gives promise of discoveries of a far-reaching and important nature. I anticipate that some future Huxley lecturer will find in this realm a fascinating theme.

In this connection may be mentioned the great pathological interest pertaining to the recent investigations of Jacoby, Conradi and others on the phenomena of self-digestion or autolysis of inflammatory exudates and necrotic material within the living body. One can readily convince himself of the energetic action of autolytic ferments by the simple experiment of placing a piece of fresh pneumonic lung in the stage of gray hepatization under chloroform and noting the rapid solution of the exudate, in contrast with the absence of this process in earlier stages of the disease. Conradi finds that bactericidal substances, to which he attaches much importance, are produced in tissues and cellular exudates undergoing autolysis.

Although my theme relates especially to the bearing of studies of immunity on pathology, it is hardly necessary to say that these studies were primarily undertaken to elucidate the great problems of predisposition and resistance to disease, and that in this field they have borne their richest fruits. It is especially gratifying to note the close convergence of the two doctrines of immunity, the cellular and the humoral, brought about by these recent discoveries. On the one hand the phagocytic school, represented so brilliantly by Metchnikoff and his coworkers in the Pasteur Institute, recognize and apply to the fullest extent in the explanation of acquired immunity the cytolytic principles based upon the cooperative action of intermediary bodies and complements. On the other hand the humoral school, led by our German *confrères*, which has been so fruitful in results of the greatest scientific and practical value, recognize the cells, and especially the leucocytes and other cells of the blood-forming organs, as the immediate source of the protective substances. There are many differences in details, especially in terminology and in interpretation, which make the divergence seem greater than it really is. The essential difference between the two schools concerns the place where the two forces, intermediary body and complement, unite. All are agreed that the intermediary body exists free in the blood plasma, but Metchnikoff strenuously insists, especially on the basis of Gengou's experiments, that the complement or cytase is within the leucocytes, from which it is not secreted but can be liberated only through damage to these cells. This question certainly needs further investigation before it can be regarded as settled.

The deeper insight which we have recently gained into the nature of the forces concerned in immunity makes especially desirable the systematic study of the blood and other fluids of human beings in health and in disease with reference to their content of specific antibodies, particularly of the bactericidal substances. It can scarcely be doubted that knowledge of this kind will be in various ways of practical value to the physician and surgeon. The simplest procedure, and the one hitherto generally adopted, is the estimation of the bactericidal power of the blood serum *in toto*. For this purpose Professor Wright* has devised an ingenious method which in his hands has furnished extremely interesting information concerning variations in the bactericidal power of the blood as regards the typhoid bacillus in health, under the influence of fatigue, in the course of typhoid fever and after antityphoid inoculations. The older methods, however, while not without value, do not inform us of the total content of the blood in immunizing substances, and have led to very discordant results, particularly as to the influence of infection upon the bactericidal power. Thus Conradi† finds, in opposition to most previous experimenters as well as to the later results of Wilde, that infection with the anthrax bacillus does not at any stage influence materially the bactericidal properties of the blood.

A useful and readily applicable method for the determination separately of the intermediary bodies and of the complements of human serum is urgently needed. When one takes into consideration the plurality of complements and of intermediary bodies, the fallacies of interpretation which may arise from failure to take account of anticomplements, of anti-immune bodies, of complementoids, of amboceptoids, of deviation (*Ablenkung*) of complements, and other principles in this complicated subject, it is clear that the problem is not an easy one.

Notwithstanding these difficulties, work has already begun along these new lines, and has led to interesting results. We

* A. E. Wright, *Lancet*, 1898, I., p. 95; 1900, II., p. 1556; 1901, I., pp. 609 and 1532, and 1901, II., p. 715.

† Conradi, *Zeitschrift für Hygiene*, 1900, XXXIV., p. 185; 1901, XXXVIII., p. 411.

know that the content of the blood in specific antibodies, and especially in complements, varies in significant ways under diverse conditions, as in infancy and in adult life, in health, in different states of nutrition, under the influence of fatigue, of inanition, of pain, of interference with respiration, of alcohol, and in disease. The infant comes into the world with protective antibodies in the blood smaller in amount and less energetic than those possessed by the healthy adult. It is an important function of the mother to transfer to the suckling through her milk immunizing bodies, and the infant's stomach has the capacity, which is afterwards lost, of absorbing these substances in an active state. The relative richness of the suckling's blood in protective antibodies, as contrasted with the artificially-fed infant, explains the greater freedom of the former from infectious diseases.

The important question of the influence of preexistent disease in predisposing to infection has been brought nearer to a solution by recent studies of immunity. Schütze and Scheller* have demonstrated that, while the normal rabbit promptly regenerates the complements used up in consequence of the injection of hæmolytic serum, a rabbit infected with the hog cholera bacillus has lost this capacity. My former pupil, Dr. Longcope, has kindly placed at my disposal the unpublished results of an investigation which he is making under Professor Flexner's direction at the Pennsylvania Hospital of the intermediary bodies and the complements in human blood in different diseases. Colon and typhoid bacilli are used as the tests, as, unless one accepts Bordet's doctrine of the unity of complements, it is more important for the study of problems of infection to determine bacteriolytic rather than hæmolytic antibodies. One of the earliest results of the systematic bacteriological examinations which we make at all necropsies at the Johns Hopkins Hospital was the recognition of the great frequency of terminal infections, formerly often undetected by the clinician, in chronic diseases, particularly of the heart, the blood vessels, and the kidneys. Dr. Longcope finds, although not regularly, still in many cases of these diseases a marked reduction in the quantity of complements, which may amount to a total loss of the colon complements. The analysis of the cases brings out unmistakably a definite relation between this loss of complement and the predisposition to infection.

The study of a series of acute infections, chiefly of a surgical nature, shows that in the course of the infection complements are being constantly used up and regenerated, and that at any given time there may be an excess or a reduction of the bacteriolytic power of the blood. Thus far it has been found impossible in these acute infections to attach any prognostic significance to the amount of complement or of bacteriolytic power, nor could any definite relation be determined between the leucocyte count and the content of complements.

Although we have traversed, gentlemen, in this lecture a path which I fear has seemed to you a long and winding one, I am conscious that I have been able to point out the features of the prospect only imperfectly and incompletely. The extent and the richness in details have been embarrassing. I trust, however, that I have been able to indicate in some measure the great interest and importance to biology, to physiology, to pathology, to every department of medical science and art of investigations which have led to a deeper insight into certain manifestations of cellular life. What has been conquered by

* Schütze and Scheller, *Zeitschrift für Hygiene*, 1901, XXXVI., pp. 270 and 459.

these investigations is simply a bit of new territory pertaining to the intimate life of the cells, and we find here, as whenever we are able to penetrate deeper into this life, that there comes a flood of new light into every department of biology. The researches on immunity, which to some of short vision once seemed to threaten the foundations of cellular pathology, have served only to strengthen them. These researches, which have already led to the saving of thousands of human lives, and will lead to the saving of untold thousands more, have been carried on by the experimental method, and can be conducted in no other way. This method is as essential for the advancement of medical science as for that of any of the natural or physical sciences. To restrict unnecessarily and unjustifiably its use is nothing short of a crime against humanity. It is an evidence of the robust vitality of English physiology and medicine that in spite of unwarrantable obstacles thrown in their path their contributions to science in recent years have been so numerous and so important. The influence of English thought and action is great with us in America. See to it, my colleagues and men of science in the British Isles, that you retain for yourselves and hand down to your successors, at least without further impairment, the means of promoting medical knowledge and thus of benefiting mankind.

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SCIENTIFIC BOOKS.

International Catalogue of Scientific Literature; first annual issue—M, Botany. Published for the International Council by the Royal Society of London. London, Harrison & Sons, 45 St. Martin's Lane. Vol. I., Part I. May, 1902.

For some years the Royal Society has had under consideration the preparation of a complete index of current scientific literature, which now has materialized to the extent of a thick pamphlet of 378 pages, designated as 'part I., of volume I.' The part before us is devoted to botany, and from it we may make an estimate of the probable value of the complete work. The preface discusses the magnitude of the undertaking, and the inadequacy of a mere authors' catalogue, scientific workers needing subject indexes as well. This task being far greater than the Royal Society alone could undertake, international cooperation was sought, resulting in a conference of delegates in London, July, 1896. At this conference 'it was unanimously resolved that it was desirable to compile and publish, by means of an international organization, a complete catalogue of scientific literature, arranged according both to subject matter and to authors' names, in which regard should be had, in the first instance, to the requirements of scientific investigators, so that these might find out, with a minimum of trouble, what had been published on any particular subject of inquiry.'

Subsequent conferences were held in 1898 and 1900, the result being the appointment of an international council, the establishment of a central bureau in London, and the undertaking of the Royal Society to act as the publishers of the catalogue on behalf of the council. Provision is made for an international convention, which is to have supreme control over the catalogue, and which is to meet in 1905, and again in 1910, and every tenth year afterwards. It is to 'reconsider, and if necessary, to revise the regulations for carrying out the work of the catalogue.'

Seventeen branches of science are to be included in the whole catalogue, and these are arranged under the letters of the alphabet as follows: A, mathematics; B, mechanics; C, physics; D, chemistry; E, astronomy; F, meteorology; G, mineralogy; H, geology; J, geography; K, paleontology; L, general biology; M, botany; N, zoology; O, human anatomy; P, physical anthropology; Q, physiology; R, bacteriology. In this scheme physiology is made to include experimental psychology, pharmacology and experimental pathology. "Each complete annual issue of the catalogue