carriers among the troops. Thus, in one regiment a carrier was discovered in the regimental kitchen. In another, which had lately received reinforcements, no less than 96 men had to be examined before the carrier was found. But the source of infection was not always in the troops. The part of Flanders that we held was a hotbed of enteric, and many cases were found in the civil population. The search for these, in which the bacteriologists were aided by the Belgian sanitary officer, Dr. de Wulf, and also by the Society of Friends, was very difficult. In one village cases of enteric occurred in three successive formations that were billeted there. No civil cases could be traced, until news was brought of a child that had been sent away to convalesce at a neighbouring farm. The clue was followed, and the family to which the child belonged were identified as the source of the outbreak. They kept an estaminet, and sold food to the soldiers. Many carriers of dysentery have also been discovered and isolated.

The conditions of warfare made it far less possible to obtain contacts of cerebro-spinal fever at the front where men are constantly moving, than it is at home where a man may be stationary for weeks.

The subject is extremely difficult, and even now the method of diagnosis that satisfies one bacteriologist is held insufficient by another. I do not remember any instance in which we could connect two cases of the fever as cause and effect, or as caused by the same infection. They have been very uncommon, even under the conditions at home.

As instances of the examination of new or little known forms of disease, I may mention trench fever,¹ investigated by Captain McNee; spirochaetal fever,² by Captain Adrian Stokes; gas gangrene;³ and the histology of the prevalent nephritis, by Lieutenant Dunn.⁴

As these researches will no doubt be dealt with under their separate headings, it needs only to refer to them here as examples of excellent work done in the laboratories of the front and of the importance of this organization.

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TRENCH FEVER AND ITS ALLIES.

BY

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In the first winter of the war there were many cases of stiffness and pain in various parts, especially in the muscles of the back and shoulders, with some fever, and there were also a few cases which were thought to be influenza, but in the spring of 1915 our attention was drawn to the frequency of a form of fever which struck every one as novel. The men were often seized suddenly, perhaps when performing a duty, with a vertigo or faintness so severe as to drop them in their tracks. A severe headache, especially at the back of the eyes, and a pain in the back began almost at once. Occasionally there was pain in the left hypochondrium. When the men reached the clearing station they complained of much pain in the legs, especially down the shins. Many could not bear the pressure of the bedclothes. In some the pain was rather in the muscles of the thigh, and in a few it was felt in the calf. Along with these symptoms the tongue was furred, the appetite bad, nausea was not infrequent, and the bowels were constipated. There was no cough, and the lungs were unaffected. The pulse was from 70 to 80, and the heart was natural. The spleen was not enlarged, and there was no albuminuria. The temperature rose quickly, reaching 102° F. or more on the second day. Occasionally the temperature rose to 105° F., and was accompanied by stupor. It fell on the third and fourth to normal, and then in many cases rose again on the fifth or sixth day, to fall again on the ninth or tenth. This saddle-backed curve resembled that of the phlebotomus fever of the Mediterranean, and the symptoms were not dissimilar, though milder, but there was no phlebotomus in this country.^{1 2}

As further cases were observed, it was discovered that the relapse might take place at different intervals, even

after ten days of a normal temperature, but that for each patient the cycle was regular. Thus in one patient the cycle might be seven days, in another ten, and in another even thirteen days. The periods of normal temperature lasted five, eight, and eleven days respectively, and were interrupted by a sudden fever, which might rise to 104° F. and as quickly disappear. As the disease continued the fever rose each time to a gradually lower level, and the intervals might become longer.³

In a large number of cases there was only one bout of fever. Many had only one relapse, but if there was more than one there were frequently many, and such a patient might continue ill for many weeks.

Such charts as these, with a sharp and sudden rise, separated by regular and afebrile periods, were strongly suggestive of the life-cycle of some blood parasite, and every method was followed which gave hope of its discovery. Up to the present no such body has been found, but it has been shown that the fever can be communicated by the blood from a patient if injected into a healthy man, and, further, that the virus is connected with the red blood cells and not with the serum. It has been a common opinion that whatever the virus may be it is conveyed by the louse, and there are a few facts to support this.⁴

No case proved fatal, and the great majority made a speedy recovery, but some were left with irregularity of the heart, which persisted for a long time. Cases of recurrence after intervals of good health were not unknown; it was evident that one attack did not produce immunity.

Many drugs—including the salicylic acid compounds, and quinine by the mouth, and salvarsan, and antimony by injections—were tried. None had any effect upon the course of the fever. In a few cases aspirin, and in more morphine, relieved the pain temporarily.

Along with this relapsing form, which was called trench fever, there were others which showed no relapse, though the symptoms were the same. Some of them had a hog-backed curve, the highest points lying towards the middle of the curve, which fell to normal about the tenth day. Others had a low pyrexia, never rising much above 100° F., but lasting a fortnight or three weeks. In the summer of 1916 a number of cases of short fever were seen in which the spleen was enlarged. These cases were occasionally observed at other times. They were probably a special form.

Some thought that they could distinguish a special type which they called shin fever, but this could not, on wider investigation, be established. It should be added that pain in the shins was not peculiar to any fever. It was seen in typical cases of enteric.

Some bacteriologists found various infections in the blood of these cases, but their results were not confirmed.

The chief diseases from which these fevers had to be distinguished were one of the enteric fevers and influenza. It was not until repeated examinations, extending over some hundreds of cases, had been made that we felt justified in excluding the former. Influenza is so protean a disorder that its exclusion was still more difficult. There were in these fevers, however, no catarrhal symptoms, the *B. influenzae* was never found in the blood, and the cases occurred only at the front or among the personnel of hospitals where the cases were treated. It was not a general epidemic as influenza usually is.

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BIOCHEMISTRY AND WAR PROBLEMS.

BY

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THE application of science to every department of modern warfare is universally appreciated. Without the co-operation of the engineer, the physicist, and the chemist, warfare could not approach its present destructive character. But, apart from these activities, the importance of which can hardly be over-estimated, a large amount of purely scientific endeavour has been devoted to the conservation of the health of those taking an active part in the present struggle. The object of the following notes is to indicate

a few striking examples of what may be termed constructive applications of biochemistry.

PURIFICATION OF WATER.

The supplying of a large army in the field with safe and palatable drinking water is obviously a problem of immense practical importance. The difficulties encountered, particularly when troops are living in typhoid-infected areas, were great, but the sanitary service of the army has every reason to feel proud of the great success it has achieved in this direction. The use of chlorine compounds for the sterilization of polluted waters has long been practised, particularly in typhoid-infected areas in America, but the application of the method on a huge scale to field conditions required additional experience and experiment. The care bestowed in the control of the army water supplies by both chemical and bacteriological methods has been fully justified by the results, and if the publication of statistics were permitted, it would appear that some other nations had still much to learn in this direction. While the excellent typhoid statistics of the British army are doubtless in large measure due to protective inoculation, the efficient supplementing of this procedure by the provision of safe water supplies is no inconsiderable factor.

ACCESSORY FOOD FACTORS (VITAMINES).

Questions of diet are of no less importance than water supply. In recent years biochemical studies have indicated the necessity of the presence of certain substances in relatively small amounts in order to make an otherwise ample diet adequate for maintenance or growth. The earliest experiments of this kind were made at Cambridge by Professor Hopkins and Miss Wilcox. They found that mice furnished with a diet containing liberal amounts of fat, carbohydrate, and protein, which were much more than sufficient to furnish the energy requirements of the organism, failed to sustain life if a particular amino-acid, discovered by Hopkins, was not a constituent of the protein. This heterocyclic amino-acid, tryptophane, systematically named indole α -aminopropionic acid, was found as a constituent of many proteins, but not all. It is absent, for example, from gelatine, this being one reason why gelatine is an incomplete protein food. Hopkins and Wilcox found that addition of small amounts of tryptophane to the inadequate diet just referred to was followed by marked improvement in the condition and duration of life of experimental animals. A most valuable discussion on the importance of individual amino-acid groupings in proteins for nutrition and growth has recently been published by Hopkins in his lecture at the Chemical Society, May 18th, 1916.¹

Later experiments showed that young animals could not grow when fed upon so-called "synthetic" diets consisting of mixtures of pure proteins, fats, carbohydrates, and salts, although maintenance might be secured for a considerable time. But Hopkins² found that a substance or substances found in normal foodstuffs (for example, milk) can, when added to the dietary in astonishingly small amounts, secure the utilization for growth of the protein and energy contained in such artificial mixtures. The significance of these observations with regard to diseases such as scurvy, rickets, and beri-beri was at once apparent.

Late work by Hopkins, and a host of followers, has served to emphasize the importance for nutrition and growth of these small amounts of substances which are often called "accessory factors" or "vitamines." Some of the substances which are found in milk, yeast, whole rice meal, and animal tissues, are extraordinarily potent in the relief of polyneuritis induced experimentally in birds by feeding on a "vitamine"-free diet of polished rice. The exact nature of these substances is still obscure, although Funk,³ working at the Lister Institute, Suzuki in Japan,⁴ Moore and co-workers,⁵ Cooper,⁶ and others, in England, have obtained partly purified basic products of high potency. The practical importance of these studies has been amply justified by the success obtained in the prevention of scurvy, beri-beri, and similar nutritional disorders among troops operating under conditions which render the abundant supply of fresh food difficult or impossible. By supplementing the diet available under such circumstances with small amounts of material rich in "vitamines," it has been possible to restrict the development of the disorders mentioned in a way that would have been impossible even

a few years ago. A large number of experiments as to the most practical form of supplying the needed vitamins has been carried out under the direction of the authorities concerned, who were keenly alive to practical lessons to be learnt from the laboratory studies just referred to.

It is of interest to note that some recent experiments of Williams⁷ upon the curative action of various substances on experimentally induced polyneuritis in birds appear to show that certain synthetic pyridine derivatives containing a betaine-like ring possess this property in high degree. A substance intimately related to the purin compound adenine has been isolated from yeast, and also found to exert curative action. The necessity for purin derivatives for the synthesis of nuclear substance *in vivo* is noteworthy in this connexion. It may reasonably be expected that the more intimate analysis of metabolic processes which is being made possible by the pioneer work of Hopkins will find many applications in the treatment and prevention of nutritional disorders.

WOUND INFECTIONS.

Few subjects have attracted more urgent attention during the present war than the question of the treatment of infected wounds. As every one knows, this problem has surpassed in difficulty anything which had previously been experienced, both as regards the frequency and malignancy of wound infections. Apart from special surgical procedure and protective inoculation, with which we are not concerned at the moment, the problem has been chiefly attacked in two ways.

Hypertonic Salt Solutions.

The method advocated by Sir Almroth Wright demands the employment of salt solutions of varying concentration but of slight germicidal action. Hypertonic salt solutions are used to provoke an increased flow of lymph from the wound surfaces with the object of facilitating and accelerating the natural processes of repair. The other methods which are in vogue involve the use of more active chemical agents—antiseptics—with the aim of reducing infection by more or less direct germicidal action. There has been a great deal of discussion as to the rival merits of the two systems, but to some observers at least it would appear that the differences between the so-called "physiological" and "antiseptic" methods of treating wounds are not nearly so great as at one time appeared, and that the effects sought by the best exponents of the two methods have much in common.

Antiseptics.

At first, prime importance was attached to the search for the most actively germicidal substances as judged by their action on micro-organisms suspended in various media outside the body. With the aid of these substances much was expected in the way of rapid wound sterilization, but the results were mostly disappointing. The problem was evidently not to be solved in this way, and the idea that dirty lacerated wounds could be sterilized by isolated applications of powerful antiseptics had early to be abandoned. The exponents of physiological methods did genuine service in indicating the danger and futility of such a procedure, and it was soon realized that where, as was the rule, sterilization was not effected, the concomitant injury to living tissue by the unintelligent application of corrosive antiseptics might far outweigh any advantage gained. But at the same time it cannot be too strongly insisted that experiences of this kind cannot be taken as refuting the value of every kind of antiseptic treatment. With the desire to secure crucial experiments to prove the inutility of antiseptics, wounds have been extensively swabbed with pure carbolic acid with the avowed intention of giving the antiseptic every chance. Yet, in the light of the experience of the last thirty months, the finding of organisms in the discharge from any but trifling wounds treated in this way was almost a foregone conclusion, and proves nothing as to the efficacy of antiseptics in general when employed under proper conditions.

When it was realized that the immediate sterilization of badly infected deep wounds by a single application of a "strong" antiseptic, even when applied soon after the infliction of the wound, was rarely successful, attention was turned to the repeated or even continuous application

of relatively mild antiseptic solutions, and here genuine success appears to have been obtained.

Hypochlorites.

Of the innumerable antiseptics which have been employed in the present war two appear to have been regarded with especial favour, and they have much in common. These are the calcium hypochlorite and boric acid mixture introduced by Professor Lorrain Smith under the name of "eusol,"⁸ and neutral sodium hypochlorite solution, the preparation of which was described in this JOURNAL.⁹ The composition of the latter solution has been modified by various writers in minor details without much essential change. Although the germicidal action of hypochlorites has long been made use of for water purification and other similar hygienic purposes, until recently they had seldom been used for surgical purposes, except occasionally for the removal of sloughs. One reason for this is undoubtedly to be found in the fact that commercial hypochlorite preparations commonly contain free alkali, and hence are intensely irritating. The presence of free alkali is guarded against in the preparation of the two solutions just mentioned by substantially the same method, which may be incidentally referred to as illustrating the application of a well-known physico-chemical principle. It has long been known that when a polybasic acid, such as phosphoric or carbonic acid, is partly neutralized by successive additions of alkali, a point is reached when the solution contains a mixture of acid and neutral salts which reacts approximately neutral to suitable indicators. No such a solution moderate additions of either acid or alkali may be made without changing the reaction of the solution, the only change being variations in the proportions of various salts. This mechanism, as Henderson and others have shown, is largely responsible for the maintenance of the essential neutrality of blood and other body fluids under changing conditions. In the case of the antiseptic solutions under consideration, the polybasic boric acid was chosen for adding to the alkaline hypochlorites, so that the resulting solutions were capable of maintaining neutrality. Using similar principles, Daufresne has developed a hypochlorite solution containing no boric acid but a mixture of carbonate and bicarbonate. Such solutions are referred to as "buffer solutions," indicating their ability to reduce the actual change of reaction due to the addition of either acid or alkali.

These hypochlorite preparations are probably used more widely than any other antiseptic solutions at the present time, not only in our own Army Medical Service but in the allied countries, and from recent reports it appears that the Germans have been making extensive use of them as well. They were both developed as the result of work carried out on behalf of the Medical Research Committee. The wide adoption of these antiseptics in preference to those more generally used prior to the war is significant, especially in view of the disfavour with which antiseptics in general were regarded a short time after the outbreak of the war, as a result of their comparative failure to meet the demands then made upon them.

This preference for the hypochlorite antiseptics as compared with many others appears to be supported by both clinical results and by laboratory investigations. The solvent action of hypochlorites on necrotic tissue is a great advantage when contrasted with the coagulating effect of many antiseptics on blood serum and wound exudates. The former action of hypochlorites permits the wound surface to remain moist and so removes obstacles to the outward flow of lymph, which is so readily checked by antiseptics which are protein precipitants. Moreover, the hypochlorites, by virtue of their strong oxidizing power, appear to react readily with the toxic products of bacterial activity—and indeed this action, as will be referred to later, has been used by Dean for the preparation of dysentery toxin of greatly diminished toxicity, but otherwise potent for the production of antibodies. The diminution in general toxæmia following the free use of hypochlorite in old, badly infected wounds, especially fractures, in which sterilization is incapable of attainment, is a common observation, as well as the increase in the toxæmia following its abandonment or replacement by some other solutions. Furthermore, from the experiments of Wright,¹⁰ it appears that hypochlorites are preferable to antiseptics such as phenol or iodine, since they differ markedly from the latter in being less disturbing to a

favourable balance between the antitryptic and tryptic effects in fluids such as are formed by wound secretion. Wright regards this as the probable explanation of why wounds treated with hypochlorite suppurate less and heal better than did the wounds treated in the earlier period of the war with the antiseptics then in use. The suggestion that antitrypsin plays an important part in the normal bactericidal properties of blood, as put forward by Wright and others, has an obvious connexion with the above opinion, and in this relation it may be recalled that hypochlorites, like many other active chemical substances, when injected intravenously into animals, produce first a fall and then a marked rise above normal of the antitryptic value of the blood serum.

Synthetic Dyes as Antiseptics.

The selective antibacterial action of certain synthetic dyes (crystal violet, malachite green, etc.) has long been applied by bacteriologists in the preparation of differential culture media. The work of Ehrlich and his school on the specific therapeutic action of certain dyes in protozoal infections is also well known. The special need created by the war for substances of low toxicity to the tissues of higher animals, but of high antiseptic potency, has led to the use of several dyes for the disinfection of wounds. Very good results have been obtained by using dyes of the triphenylmethane series (crystal violet, malachite green, brilliant green). Fildes, Rajchman, and Cheate,²⁸ who were among the earliest workers to apply the disinfecting action of such dyes to wound treatment, used a mercury compound of malachite green, sprayed on to the wound surface in alcoholic solution, and obtained better results than with either malachite green or mercuric chloride alone. A recent publication by Browning²⁴ deals with a further development of the use of dyes as antiseptics, and describes results of extraordinary interest and promise, obtained with a dye of the acridine series, of which the trypanocidal value was studied some years ago by Ehrlich. This substance, "trypaflavin" (diamino-methyl acridinium chloride), has been found to have a high general antiseptic value by Browning, who, on account of this more general application, proposed to call it "flavine." Browning finds that, while the antiseptic action of all other substances examined, including the dyes mentioned above, is greatly diminished by the presence of blood serum, that of flavine is not only not diminished, but is conspicuously increased, even to five times its potency in water. This, taken in conjunction with Browning's further observation that flavine is harmless to the tissues, and even to the activity of leucocytes, in concentrations having a strong antiseptic action, awakens great expectations concerning its therapeutic value in various infections. Preliminary trials have already confirmed its efficacy in the treatment of septic wounds, and the results of the more extended trial, which will be carried out under the Medical Research Committee as soon as adequate quantities of the dye are available, will be awaited with interest.

THE CHEMISTRY OF DISINFECTION.

But the measure of success achieved by many surgeons in the treatment of infected wounds with hypochlorite antiseptics has been due to much more than the substitution of one antiseptic lotion for another. Granted that hypochlorites possess certain advantageous properties not shared by other antiseptics, their employment requires the observance of other essential conditions if success is to be obtained. The development of these conditions, apart from the necessary surgical interference, was based on laboratory work. The researches of C. J. Martin and Miss Chick have done much to supply accurate information as to the laws of disinfection. From studies on the rate of disinfection by mercuric chloride, silver nitrate, and phenol acting on *B. paratyphosus* and spores of *B. anthracis*, Miss Chick¹¹ concluded that a very complete analogy existed between ordinary chemical reactions and the process of disinfection, one reagent being represented by the disinfectant and the second by the protoplasm of the bacterium. In the case of the spores the process of disinfection proceeds with a reaction velocity in accordance with the well-known equation for a unimolecular reaction, if figures representing "numbers of surviving bacteria" are considered and taken as the equivalent of "reacting substance." In the case of *B. typhosus* departures from the simple law were noted owing to permanent differences

in resistance to the antiseptic among the individual organisms. The rate of disinfection in all cases was greatly increased by rise in temperature, the velocity being increased three to ten fold by an increase of ten degrees Centigrade.

If the act of disinfection be thus regarded as a chemical reaction proceeding with a definite velocity, the successful use of antiseptics will depend on the establishment of conditions such that the reaction may be pushed as far as possible towards completion in any given period of time. Increase in the active mass of antiseptic and rise in temperature will favour the course of the reaction, but in the case of wound treatment these factors are obviously limited by other considerations. In the case of hypochlorites, the maintenance of an effective mass of antiseptic in a wound cavity is a difficult problem on account of the ease with which these substances enter into combination with proteins and other compounds in the wound exudate. Of these products, those which contain active chlorine united to nitrogen retain their germicidal action while the others lose it entirely. It is for this reason that the technique employed by those who obtain really satisfactory results with the hypochlorite antiseptics requires such careful observance. The repeated renewal of hypochlorite solution in wounds which have received adequate preliminary surgical treatment is a practical necessity that is easily understood if the rate of its disappearance is borne in mind, but this has too often been overlooked by those who hope to find special curative action following infrequent administration of these antiseptics. The technique employed by Carrel and Dehelly in France and by Sir Berkeley Moynihan¹² and many others in England, by which frequently renewed quantities of hypochlorite—the amount varying with the character and surface extent of the wound—are injected into the cavity and its recesses by means of rubber supply tubes, is a natural consequence of the chemical properties of the antiseptic they employ. As in the case of the treatment of wounds with hypertonic salt solution and other irrigation methods the technique is of prime importance, and success or failure depends to a greater extent upon this than upon minor details in the composition of the solution.

The widespread adoption of hypochlorites for antiseptic purposes invited chemical studies as to their mode of action. Apparently there are great differences in the way antiseptic substances act. Miss Chick's experiments confirmed the view that the metallic ions resulting from the electrolytic dissociation in solution of salts such as mercuric chloride and silver nitrate are the real disinfecting agent rather than the salts as a whole, and this conclusion is in harmony with some unpublished results showing that some double cyanides of silver which do not dissociate normally have a surprisingly low germicidal action. Cooper,¹³ working at the Lister Institute, concluded that the germicidal action of phenol is not due to a typical union of the phenol with bacterial protoplasms, as is probably the case with formaldehyde, but rather to a de-emulsifying effect upon a colloidal suspension of some constituent protein essential for the vitality of the organisms. In the case of hypochlorites direct chemical action upon bacterial proteins, and any other protein which may be in the medium, undoubtedly occurs, and the germicidal substances so formed may contain much active chlorine linked to nitrogen as-NCl groups. A systematic study of many synthetic substances containing this grouping led to the conclusion that almost all of them possessed high antiseptic properties, and one of them, toluene sodium sulphochloramide, or chloramine-T, has been used on an extensive scale. Its manufacture was first undertaken in England, and it is now made by many firms here and abroad. Apart from the use of the substance for general antiseptic purposes, its stability permits its use in very dilute solution under conditions in which hypochlorites would be too irritating. One of the most interesting applications of this substance has been worked out by Colonel Gordon and published in this JOURNAL. Carriers of the meningococcus, when placed in an inhalatorium and subjected to the action of a steam spray carrying the antiseptic in fine suspension, have been freed from this organism in satisfactory manner, and the successful extension of the method to other infections of the upper respiratory passages seems likely. Here again, as in the use of antiseptics for wound treatment, details

of technique in the presentation of the drug are of cardinal importance.

SYNTHETIC DRUGS.

Among the many tasks which confronted chemists at the outbreak of the war, few were more urgent than that of preparing adequate quantities of certain drugs for the supply of which we had previously been dependent on hostile countries. Much of this work has been done in a successful and unobtrusive way in the laboratories of chemical manufacturers, while in other cases the assistance of organic chemists on the staff of our universities has been freely and cheerfully given. It is unnecessary to go into details with regard to the individual products, which cover a wide range, but, as is well known, the demand for arsenical compounds of the type of salvarsan and various local anaesthetics such as novocain and eucaine was particularly heavy and has been well met. It will be recalled that the latter substance is an acetone derivative, and in this connexion reference may be made to the development in this country, since the war commenced, of the industrial production of acetone by a fermentation process. This new industry promises to be of great utility. Salvarsan and its congeners and the local anaesthetics are now produced in a thoroughly successful fashion not only in this country but also in Canada. The control of the quality of salvarsan offered for sale in this country has been cared for by the Medical Research Committee, while in Canada the manufacturers' product is tested in the laboratories of the Pathological Department of Toronto University.

An interesting investigation on the fate of salvarsan and neo-salvarsan has recently been published by W. J. Young.¹⁴ This author finds that these substances, when injected intravenously into goats, give rise to the presence of arsenic in the blood plasma and corpuscles in a form which cannot be removed by dialysis but which can be precipitated with the serum proteins by tannic acid. A similar behaviour is shown by atoxyl. No such combination could be observed when inorganic arsenic preparations were injected, and it would appear as if the varying therapeutic effects of different types of arsenic preparations depended, at least in part, on whether non-dialysable arsenic appears in the blood. Careful studies of the rate of arsenic excretion following administration of salvarsan and neo-salvarsan have been published by Webster.¹⁵

Although so much remained to be done to supply existing demands, a few new therapeutic products of approved value have been introduced. Among these mention must be made of the introduction of emetine bismuthous iodide by H. H. Dale¹⁶ for the treatment of carriers of amoebic dysentery. This substance was suggested by Du Mez as of possible value, and Dale's work has definitely shown that carriers who have long been treated without success with emetine administered hypodermically in the ordinary way, can be freed from infection by the new drug, which, unlike emetine itself, can be given by the mouth.

A new synthesis of β -iminazoletylamine, a substance which was shown by Barger and Dale to be one of the most physiologically active constituents of ergot, has come to light in a rather curious way. In studying the oxidizing action of the antiseptic chloramine-T upon various amino acids derived from proteins, it was found that many of these substances were converted into cyanides with one less carbon atom than the original substance. Histidine, for example, gave cyanomethylglyoxaline, and the latter substance, as was already known, gives the active β -iminazoletylamine on reduction.¹⁷ The reaction promises to be of technical value for the preparation of this and allied physiologically active amines.

PHARMACOLOGICAL RESEARCH.

In relation to pharmacological research, reference must be made to an extraordinary investigation in the chemistry of the opium alkaloids recently published by W. H. Perkin.¹⁸ The work mainly deals with cryptopine, an alkaloid occurring in such small quantities that 10,000 lb. of opium were needed for the preparation of 5 oz. of the hydrochloride. The breaking down of cryptopine, mainly by oxidation under carefully regulated conditions, with the formation of substances either of known structure or which were subsequently synthesized, and the deduction of the probable molecular arrangement of the parent alkaloid from the structure of these simpler derivatives, is a triumph

of experimental skill and theoretical insight. Scores of new compounds were carefully characterized in the course of the work, which throws much interesting light not only on the structure of cryptopine and protopine, but on other related alkaloids. It is of course unnecessary to refer to the fact that it is to researches such as these that we owe inspiration and direction, not only in the work of the synthetic preparation of the natural alkaloids of therapeutic value, but in the artificial synthesis of new drugs.

Cushny¹⁹ has lately made some noteworthy observations on the pharmacological antagonism existing between atropine and pilocarpine. These experiments were made on the salivary secretion, and showed that in different dogs a constant amount of atropine was necessary to oppose the action of a constant amount of pilocarpine, and in the same dog the ratio of the two drugs remained the same, irrespective of how the actual amounts injected might vary. It appears, therefore, that the antagonism proceeds according to the laws of mass action rather than those of simple chemical combination in definite proportions. The investigation is an interesting example of the application of physico-chemical methods to the elucidation of the mechanism of the action of drugs.

ANTITOXIC SERUMS.

Reference has already been made to the discovery by H. R. Dean and R. S. Adamson²⁰ that the toxicity of Shiga dysentery vaccines could be enormously reduced by the restricted action of hypochlorites and other oxidizing agents without lowering their immunizing power. This gratifying and rather surprising result has been abundantly confirmed, and points the way to a number of other allied problems of practical importance which might be successfully attacked, especially if an adequate analysis of the chemical reactions concerned should result from further investigation.

One result of the war has naturally been an enormously increased consumption of various antitoxic serums. The concentration of serums by the use of fractional precipitation of the contained proteins by salts such as ammonium sulphate has led to the preparation of high titre serums from which much of the inert material has been removed. In a recent communication from the antitoxin laboratories of the Lister Institute at Elstree, Miss Homer²¹ has described a number of practical improvements in the methods originally developed by Banzhaf and Gibson, which promises to make the method easier to carry out and to give more uniform results.

Theoretical studies by Dale and Hartley²² on the relation of anaphylaxis to different serum proteins offer some practical considerations. They show that each and all of the individual proteins of a serum can act as anaphylactic antigens, and that the ideal to be aimed at in concentrating the curative elements in a specific immune serum is simply the reduction of the ratio of total protein to antitoxic value. For the purpose of reducing serum reactions the elimination of albumin appears to be as important as that of the cuglobulin when, as is usually the case, the pseudoglobulin is the fraction carrying the therapeutic power. Dale and Hartley find that the latent period of sensitiveness to albumin is relatively long compared with the globulins, and this may have a bearing on the successive crops of serum rash which have been recorded as following a single injection of serum.

PROTECTION AGAINST POISONOUS GASES.

In closing, reference must be made to an extremely important branch of biochemical work about which, for obvious reasons, little can be said. The introduction of gas warfare by an unscrupulous and inhuman foe at once led some of the ablest chemical and physiological investigators in the country to devote their energies to devising the best methods of protection against asphyxiating gas and lachrymatory shells. The ingenuity displayed by the enemy in employing every conceivable means of chemical attack has been steadily met by corresponding improvements in methods of protection. These researches, often conducted at considerable personal risk, have presented problems calling for rapid solution, which demanded the highest grade of scientific work, and it is unfortunate that more cannot at present be written of the admirable way in which these problems have been solved. No line of scientific endeavour is more appealing than that of giving

to our own and allied soldiers the best possible protection against this barbaric form of attack, and the success that has been attained must be universally appreciated.

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The Croonian Lectures

ON

ADAPTATION AND DISEASE.

DELIVERED AT THE ROYAL COLLEGE OF PHYSICIANS,
JUNE 14TH, 1917.

By J. G. ADAMI, M.D., F.R.S.,
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LECTURE I.

INTRODUCTORY: THE BASAL PROBLEM OF EVOLUTION.

I CAN well imagine that in these critical days, had you honoured a civilian Fellow of the College with the invitation to deliver the Croonian Lectures, he would have found it difficult to offer to you material which he, and which you, regarded as reaching the standard attained by the long series of his predecessors. There is no Fellow of this College who does not find the war and its issues so all-pervading as to exclude full and uninterrupted consideration of other topics. Still less can one who has donned khaki and been given an administrative post do justice to the opportunity most graciously afforded to me. He could, it might be urged, select some branch of military medicine as his topic, but to do this while the war is in progress is to sacrifice perspective and afford an incomplete presentation. Administrative duties in the office have debarred me from sustained personal observation and research in the clinic or the laboratory. The time is not yet ripe to attack the vast mass of material bearing upon the incidence of disease in the army already collected by the Medical Research Committee at the British Museum. It will, in the first place, demand long months before that material is sorted and ready for statistical and other studies; in the second place, the policy of publication of studies of this nature during the continuance of the war may well be called in question; and, lastly, it has to be confessed that, taken as a whole, the material collected at the British Museum, while far in advance of any collected in any previous war, is nevertheless of value only for comparison with the statistics gathered in these previous wars. The nomenclature of disease employed—an abbreviation of that established and authorized by this College—is in many respects not sufficiently precise for a thorough analysis. There are, for example, many forms of acute nephritis and of valvular disease of the heart. The official nomenclature does not encourage any precise distinction between the various forms. My colleague, Captain G. Campbell, C.A.M.C., has afforded me evidence that gonorrhoeal endocarditis is more frequent in the army than in civil life; but the material collected—the index cards, medical case sheets, etc.—in itself gives no indication of this increase. In short, so far as I can see, the only way in which the material now being collected can be rendered valuable from a scientific point of view, is for specialists both here and overseas to make an intensive study of groups of individual