the material. As to the diurnal variation, was it not for the bacteriologist to inform him—a mere clinician—that unless he sent him daily specimens for three, five, seven days (it was for him to decide the number), he could not obtain any information to carry conviction to his own mind? These were matters of technique. All his three bacteriological colleagues who sent these differing reports sent him vaccines or were prepared to do so with great conviction as to their benefit to the patient; but they were different vaccines! There must be something wrong, therefore, in the liaison between the bacteriologist and the clinician, and he did not think it was entirely the clinician's fault if that liaison was not as close and as scientific as it might be. He thought that Dr. David Campbell was rather moving to the "left"—if he might put it that way—when most of them were moving to the "right," and this seemed a little odd. Dr. Campbell appeared to be trying to get cohesion again in that group of arthritics which the rest of them were trying to break up. The more thoroughly they examined the arthritic patient, clinically and bacteriologically, the more convinced they became that this group would be broken up. That there was a residue they all admitted, whatever name was given to it; it might be well not to give a name at all, or to put the name in quotation marks, so as to prevent misapprehension, but the more they investigated the individual case the more convinced they must be that the infective element was very high. The question as to whether it was a residual infection, whether some of these patients were partly carriers, and for that reason, or partly by reason of their joints being sensitized, got waves of reinfection, was very important,

and it all had a bearing upon the treatment of the individual case. One of the most important contributions to the etiology, and therefore to the therapeutics, was Dr. Mutch's reference to the flora of the lower part of the small intestine. Dr. Mervyn Gordon and he had previously referred to certain *post-mortem* observations which linked up a little with these very important observations to which Dr. Mutch referred. It reminded him of Sir James Mackenzie's lament that so many abdomens were opened and so few scientific observations made, but here was a scientific observation which would be of the utmost value. Dr. Mutch had not told them about the question of controls, but there was no doubt that he would report in due course. The types of patients mentioned by Dr. Heald were interesting and important. Dr. Heald had put somewhat systematically what he (the speaker) referred to loosely when he said that these patients fell into groups as to their nutritional and nerve state quite apart from the infective process. The type of patient should influence not only the choice of local treatment but of general treatment also; but he accepted willingly Dr. Thomson's suggestions as to the types of cases in which one should or should not give protein shock. Comment had been made on his remark that the ideal state for protein shock was the stationary case. He did not advise protein shock for the patient who was improving by any other method. Dr. Hamill's remarks were also very appropriate. Dr. Hamill had taken the wide view which he (the speaker) thought (to come back to his main thesis) the discussion had strengthened—that arthritis was a general disease with local manifestations, and for that reason the patient must be studied quite as much as the joint.

ON THE TOXIC NATURE OF THE STROMA OF RED BLOOD CORPUSCLES;

AND A METHOD OF TREATMENT OF BACTERIAL INFECTIONS
BASED THEREON.*

BY

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THE purpose of this communication is, first, to state, and to support by clinical and experimental evidence, the hypothesis that the constituents of the stroma of red blood corpuscles, when set free into the circulation by the destruction of the cell, have a toxic character and must be regarded as a factor in many diseases; and, secondly, to give an account of a method of treatment based on this hypothesis and designed to immunize the body against this cellular toxin.

Perhaps I can best introduce the subject by briefly relating the circumstances in which the inquiry originated. While on military duty in India I was struck, as all who have experience of tropical diseases must be, by the close clinical resemblance between sudden and severe attacks of malaria and bad cases of heat-stroke. Thinking that there might possibly be a factor common to these two conditions, it occurred to me that the destruction of red corpuscles might be the factor, and that the toxin responsible for the pyrexia in both diseases might be something set free from the red cells by their destruction in large numbers. Two points had to be determined: (1) whether destroyed red cells were actually toxic; (2) whether destruction of red cells could be brought about by the action of the sun. As regards the first point, evidence will be adduced later, but it may be mentioned here that Adami¹ has suggested that the pyrexia of malaria may be due to destruction of red cells rather than to any toxin produced by the parasite itself, and Brown² has shown that haematin causes chills and fever, and has suggested that some, at least, of the symptoms of malaria may be due to the action of haematin formed by the destruction of red cells. In order to decide the second point the following experiment was carried out.

Action of Sunlight on Erythrocytes.

On a day when the temperature in the shade was 104° and in the sun 120° (June, North-West Frontier Province) a test tube containing washed human red corpuscles suspended in isotonic saline was exposed to the direct rays of the sun. It was placed in a beaker half-full of water and wrapped round with lint in order to keep the temperature of the fluid approximately that of the wet bulb thermometer. At first every two minutes and afterwards at longer intervals a drop was taken from the surface of the fluid and examined under the microscope in the laboratory a few yards away. A second tube was kept in the shade and used as a control. In the tube exposed to the sun, even after only two minutes, definite changes were observed; many small globules were seen, some adherent to the red cells, others free. The number of these globules was increased in films examined later. In two hours the contents of the tube were chocolate-brown in colour and only a granular debris was seen microscopically, no whole red cells remaining. No change was seen in the control tube.

As the cells were exposed in a glass tube, which would, of course, entirely cut off the actinic rays, allowing only the heat rays to penetrate, the final change, seen after two hours, was undoubtedly due to heat alone, but the changes seen in the first few minutes, before the temperature could have been appreciably raised, were, I believe, due to actinic rays falling directly on the surface of the suspension (the tube being filled nearly to the brim and the sun being nearly vertically overhead).

It is known that ultra-violet light has a haemolytic and, to a less degree, a stromolytic action.³ Details of further experimental work with ultra-violet light are given below.

The Toxic Nature of the Stroma of Red Cells.

The first experiment to decide this point was carried out on the same day that I first exposed red cells to the sun, and was unsuccessful. The tarry material was allowed to settle at the bottom of the tube and 5 c.cm. of the brown supernatant fluid was injected deeply under the skin. Nothing happened, beyond some discoloration of the skin, and I now know that the toxic element is not soluble in saline but remains in the tarry material consisting of the broken-down cells. The supernatant fluid is brown from altered haemoglobin and is not toxic. The other experiments have been done in England.

* A paper read before the Leicester Medical Society.

Washed red cells, made up to the strength of whole blood, were heated in a water-bath to 56° C. for two hours, by which time most of the cells were broken up, and 1 c.cm. was injected under the skin of the forearm. At the same time the same amount of washed but unheated red cells was injected into the other forearm as a control. Cultures were previously taken to show sterility. The results were as follows: In twelve hours or less a brownish stain appeared around the site of injection, of the same tint as an old sunburn. A few hours later a pinkish tinge replaced and overlay the brown stain and the part became swollen and rather tender though not actually painful. This condition remained for about forty-eight hours, when the colour faded and the swelling disappeared, a small hard nodule remaining for several days. This was the usual reaction, though sometimes the swelling and hyperaemia were more marked and lasted longer. There was no appreciable general reaction. As regards the control, there was no reaction of any kind and no change except a bruised appearance around the site of injection. No indurated nodule remained afterwards.

The result of this experiment, which has been repeated many times, seemed to me strong evidence of the point I was trying to prove—namely, that the stroma of red cells is toxic to the individual from whom the cells were taken; it is, however, inconclusive, because proteins may be so altered by heat that a non-toxic substance might become toxic by being heated to 56° C. It became necessary, therefore, to use a method free from this objection.

Soon after starting this inquiry I found striking evidence in support of this hypothesis in a paper by C. J. Bond,⁴ in which he showed, working at the subject from the point of view of the activities of leucocytes, that the stroma of red corpuscles, set free from the cell envelope by grinding in a mortar, was toxic to leucocytes, whether of the same or of another individual. This observation suggested two lines on which to work: first, to isolate the stroma by mechanical means; and, secondly, to use the leucocyte as a criterion or indicator of toxicity in addition to the method of subcutaneous injection.

In all the experiments of which I shall now give a brief account I have had the great advantage of working in association with Mr. Bond, to whom I am indebted as much for his encouragement as for his great technical skill and wide knowledge of the properties of leucocytes. All the experiments with leucocytes have been carried out by Mr. Bond.

I. Washed red cells destroyed by heat (56° C.) were shown to be toxic to leucocytes, as shown by arrest of emigration and by alteration in the iodophil reaction. Unheated cells showed no toxic action.

II. Washed red cells ground to a putty-like debris in a mortar with sterilized silver sand were shown to be toxic to leucocytes and to give rise, when injected under the skin, to a reaction similar to that described as following the injection of heated cells, except that there was no brown staining. As a control in the latter part of the experiment the supernatant fluid containing haemoglobin was injected under the skin of the other arm at the same time. No inflammatory reaction occurred but a brown (sunburn tint) stain appeared. (It is remarkable that the clear red solution of haemoglobin resulting from grinding the red cells should produce a brown stain in the skin while whole washed red cells produce only the yellow-green colour of a bruise.) The supernatant fluid was not toxic to leucocytes.

III. Experiment II was repeated, substituting powdered glass for the sand and using as a control a suspension of the powdered glass. The same results were obtained, but it was found that the glass alone had a slight inhibitory effect on leucocytes.

IV. The experiment was therefore repeated with cells ground without any triturating medium. Complete destruction of cells is tedious by this method and it is difficult to prevent contamination by air-borne organisms. The leucotoxic effect was the same as in the preceding experiments and was quite definite.

V. Washed red cells were haemolysed by repeated freezing and thawing. No leucotoxic effect was observed.

VI. Cells laked by distilled water gave no reaction when injected under the skin.

VII. Action of ultra-violet light.

(1) A thin film of washed red cells was exposed on a slide to a Kromayer water-cooled mercury vapour lamp at a distance of 2½ inches, the slide being moved from time to time to ensure a thin film. In three minutes the colour of the fluid had become brownish. Microscopically no changes were observed in the red cells.

(2) 1 c.cm. of a similar suspension was allowed to fall, drop by drop, on the surface of a cylinder of ground glass placed at a distance of 2½ inches from the lamp. The exposure lasted for one hour, though, of course, any given part of the film would

actually be exposed for a very small fraction of that time. At the end of an hour the following changes were observed:

(a) Haemolysis; few unaltered cells remained, but many ghosts and disintegrated cells were seen.

(b) The fluid was definitely brown in colour.

(c) Examined with the spectroscope a broad band was seen in the position of the typical methaemoglobin band; the two oxyhaemoglobin bands could still be seen.

(d) The disintegrated cells were shown to be toxic to leucocytes.

As a control in this experiment, cells prepared in the same way were exposed to the lamp for the same length of time and at the same distance, but the quartz lens was covered with a mica film. Beyond slight haemolysis and very slight leucotoxic effect, both evidently due to slight mechanical damage to the cells from frequent dropping on the glass, no changes were observed.

[Mr. C. J. Bond then gave a lantern demonstration illustrating some of the foregoing experiments and gave a more detailed explanation of leucotoxicity. He said:

Some years ago I showed that disintegrated red cells, after grinding in a pestle and mortar, exercise an inhibitory or toxic action upon both native and foreign leucocytes when incubated with them in a closed glass cell. These observations bear on the problem of the reaction produced by the subcutaneous injection of disintegrated red cells. The next step was to show that red cells, destroyed by exposure to a temperature of 56° C. for two hours, when incubated with whole human blood exercise the same inhibitory and toxic effect on the leucocytes as that exercised by red cells disintegrated by mechanical or certain other destructive methods.

One drop of a suspension of red cells destroyed by heat was incubated with two drops of my own blood in a closed cell for half an hour. On washing away the clot in a gentle stream of normal saline the emigration field of leucocytes on the floor of the cell, instead of forming a thick carpet, was composed of a few isolated cells, some of which showed cytolytic changes. The effect of the red cell debris is to prevent the emigration of leucocytes from the incubated clot, and to bring about degenerative changes in the few cells which do emigrate and remain adherent to the slide; it is to this inhibitory and devitalizing influence that the term "leucotoxicity" is applied. The experiment has been carried out with different concentrations of red cell debris and with native and foreign blood. Thus the floor of a cell may be divided into two halves and a suspension of red cell debris allowed to dry on one half and a suspension of whole red cells on the other half. The cell is then filled with blood and incubated for half an hour. On examination after removal of the clot, a thick carpet of emigrated leucocytes will be found on the part painted with the whole red cells and only a few degenerating leucocytes on the area painted with the disintegrated red cells.

From these and other observations it is, I think, clear that the stroma of disintegrated red cells (not the haemoglobin) exercises an influence on living leucocytes which (1) if not too concentrated inhibits or delays emigration from an incubated blood clot, and (2) in higher concentrations brings about cytolytic changes in the leucocytes which adhere to the slide. There is reason to believe that the toxic property resides in the protein element of the stroma and not in the haemoglobin; for if the haemoglobin be removed the leucotoxic action is unaffected.

The following clinical observations also have a bearing on the problem of red cell toxicity. I have already shown that if two or three drops of blood taken from the finger of a patient with malaria, during a rigor, be incubated in a closed cell, very few leucocytes emigrate from the clot, and those which adhere to the slide show cytolytic changes. This paucity of emigration is not entirely due to the leucopenia in the general blood stream which may be present during the attack, because, if the clot from which the poor crop of leucocytes has been obtained be detached from the slide and gently washed in normal saline and reincubated on a fresh slide, a fresh crop of more active cells can be obtained.

I have recently confirmed these findings in several cases of general paralysis in which malaria has been induced for therapeutic purposes, and in which the emigration picture

could be observed before the injection of the malarial blood, during the pyrexial period, during the administration of quinine, and after recovery.

I have also ascertained that similar conditions obtain in paroxysmal haemoglobinuria. Thus, incubation of blood taken from the finger of a child during an attack gives an emigration picture very like that of malaria during the rigor; only a few degenerating cells adhere to the slide, and this condition remains, in a diminishing degree, for several days after the urine has become clear and free from haemoglobin. Later on, during recovery, free emigration of normal cells occurs. As I have stated elsewhere,⁵ similar conditions are found in certain other diseases, the emigration picture being unlike that seen in pneumonia and some other bacterial infections.

It is evident that the employment of disintegrated red cells as a vaccine in controlled doses with the object of immunizing the body against a toxin of red cell origin is a matter of great interest and importance.]

The toxic nature of the stroma being shown, it is now necessary to inquire by what means red cell destruction is brought about in the body in disease, in order to discover if this toxic agent is of any clinical significance. We have seen that red cells can be destroyed by the rays of the tropical sun, by the ultra-violet light, by heat, and by mechanical means. If it can be shown that bacteria have a similar destructive action the possible importance of this cellular toxin becomes apparent. It is well known that certain bacteria—for example, haemolytic streptococci—have this property.

In order to investigate this matter further I enlisted the co-operation of Dr. Mackarell, pathologist to the Leicester Infirmary, and he very kindly has carried out the following observations.

[Dr. Mackarell gave a demonstration illustrating the haemolytic properties of certain bacteria. He said:

In order to test the action of different bacteria on red cells, tubes containing 5 c.cm. of isotonic broth to which two drops of human blood were added were inoculated with the organism under observation and incubated at 36° C.; smears of the deposit were made every few hours. In this way streptococci, *B. coli*, *B. typhosus*, diphtheria bacilli, pneumococci, staphylococci, and diphtheroids, all freshly isolated, were tested. The staphylococci, many virulent strains of which were tested, the typhoid bacillus (isolated from a chronic osteitis), and several strains of diphtheroid bacilli had no apparent effect on the corpuscles, even after forty-eight hours' incubation. *B. coli* isolated from the uterus in a case of puerperal sepsis showed well marked haemolysis in four hours; some isolated from a case of cystitis took twenty-four hours to show haemolysis; while a strain isolated from the faeces caused no haemolysis at all in the first few subcultures, though by repeated subculturing and growing in the presence of human blood it haemolysed as rapidly as the one obtained from the uterus. Diphtheria bacilli caused haemolysis within twelve hours, and pneumococci took a little longer.

In all these cases a diffusion of the haemoglobin took place before the actual destruction of the cell envelope, and the haemoglobin was apparently unchanged. In the case of the streptococcus the action is somewhat different, the red cell being first broken up and the haemoglobin being altered so that the broth has a brownish tinge. These experiments tend to show that many organisms, not only the well known haemolytic ones, act upon red cells and destroy them, and probably produce some, at least, of their effect in the body by this means.

There remains the much more difficult problem of demonstrating the presence of an immune body in the serum of normal individuals who have received a series of injections of destroyed red cells, and of patients suffering from diseases associated with blood destruction.

Various methods of complement fixation were tried, using the patient's serum as the specific serum; the antigens tried were: (1) a suspension of cells destroyed by heat, (2) an alcoholic extract of red cells, and (3) an acetone extract. The results have so far been negative, though in a case of malaria (benign tertian, before administration of quinine) a deviation of two minimal haemolytic doses

was constantly obtained with each antigen. In two cases of pernicious anaemia the results were inconclusive, as on this occasion the antigen itself was anticomplementary. On the whole the results so far obtained have proved disappointing, but the failure is quite possibly due to the method of preparing the antigen. Further work will be done upon it.]

CLINICAL APPLICATION.

We now come to the clinical application of the theory which I have endeavoured to put forward. If it is true that bacteria can destroy red cells and that the effect of such destruction is to set free a cellular toxin into the circulation, one may look upon a bacterial infection as having a dual pathogenic effect—first, the effect of the specific toxin of the organism concerned, and secondly, the effect of the endocellular toxin. It may be impossible definitely to distinguish the effects of one of these factors from those of the other, but we may perhaps assume, from what we know of the results of rapid red cell destruction in malaria, that pyrexia, generally observed in most infections, is due, at least in part, to the endocellular toxin. The method of treatment that I have devised and practised is based on the view that the natural defensive powers of the body are in most cases adequate to deal with the bacterial invasion, but that they are handicapped and sometimes rendered ineffective by the debilitating effects of this secondary pathological factor. I aim, therefore, at immunizing the body against this toxin, just as by bacterial vaccines we aim at immunizing the body against the bacterial toxin. There is no reason why the two methods should not be used in conjunction, but I have hitherto not used this combined method, except in a few cases, because of the difficulty of interpreting the results. The method of bringing about this immunization is by the subcutaneous injection, at regular intervals, of a suspension of red cells destroyed by heating them for two hours at 56° C.

The method of preparing the material for injection is as follows:

Twenty cubic centimetres of blood are drawn from a vein into a sterile bottle containing 10 c.cm. of citrated saline to which 0.5 per cent. of phenol is added as an additional safeguard against contamination. (In the experiments with leucocytes the phenol was omitted.) The red cells are thrown down by centrifugalization and the serums and citrate solution replaced by sterile normal saline and made up to 20 c.cm. The suspension of red cells is then put up in ampoules containing 1 c.cm., and the ampoules heated to 56° C. for at least two hours in a thermostat. A slightly lower temperature fails to destroy all the cells; a higher temperature results in a sticky fluid which will, with difficulty, pass through a hypodermic needle. One cubic centimetre is sufficient to set up a moderate local reaction; when I have used more I have had a rather severe reaction.

I have in all cases kept to the same dose throughout a course of treatment, though it may quite possibly prove to be an advantage to increase the dose gradually. In acute cases the injection is given every three or four days, in chronic cases once a week. Children receive a small dose. As a general rule it is convenient and perhaps advisable to use the patient's own blood, though often, especially in children, it is more convenient to use one's own or any healthy blood. Mr. Bond's experiments seem to show that there is little difference in toxicity, whether the patient's own cells or those of another individual are used, though homologous cells are perhaps slightly more toxic.

RESULTS OF TREATMENT.

To test the effect of this method of treatment I have tried, as far as possible, to select cases where patients were suffering from bacterial infections against which they were making no headway, where surgical treatment had failed to bring about recovery, and where no other treatment suggested itself as likely to be of value. Up to the present I have not used it in cases where other methods are being used, because of the difficulty of interpreting the results, and consequently have not used it in puerperal fever or other very acute infections. Suitable test cases are not very common in the surgical wards and out-patient department.

Tuberculosis.

Tuberculosis of the urinary tract, unsuitable for surgical treatment, seemed to me to provide the most severe test of the efficacy of the method, being a disease where the

tendency to natural cure is slight and where the progress can be observed by bacteriological as well as clinical evidence. I have treated six such cases, two of which have only recently come under treatment and are therefore not reported here.

CASE I.

A woman, aged 28, with tuberculosis of the urinary tract, had been in a sanatorium for six months, and afterwards had had a course of tuberculin injections for another six months. When examined she had severe cystitis, tubercle bacilli were present in large numbers in the urine, and catheterization of the ureters showed that both kidneys were affected. There was an associated coccal infection. The symptoms were pyuria, occasional haematuria, painful and frequent micturition, and pyrexia. Treatment by injection of destroyed red cells (her own) was begun and continued at weekly intervals for twenty-four weeks, with an interval of four weeks after the first three months. Improvement, though gradual, was continuous and definite; tubercle bacilli could not be found in the urine after three months' treatment, and have not been found since though searched for many times; her general health has improved greatly, and she is able to do her ordinary work. She has had no other treatment except a short course of lavage of the bladder to clear up some cystitis that remained. It is now two years since treatment was begun.

CASE II.

A woman, aged 47, gave a history of painful and frequent micturition for some months, with increasing debility. Cystoscopy revealed a ragged ulcer on the right wall of the bladder and some general cystitis, partly obscuring the ureteric orifices. Tubercle bacilli were found in the urine. After twelve weekly injections tubercle bacilli could no longer be found, and have not been found since though searched for several times. Treatment was stopped but resumed a few months later as pain on micturition was complained of; she had eight more weekly injections, after which no urinary symptoms were present. I had occasion to treat her a year later for uterine haemorrhage, and examined the bladder. No trace of the ulcer could be seen and the bladder appeared to be healthy. Treatment was begun in July, 1923; at the last examination of urine in January, 1925, no tubercle bacilli were found, but pus cells and staphylococci were still present in the urine.

CASE III.

A man, aged 48, whose right testis had been removed three years previously for tuberculous disease. He was admitted on account of occasional haematuria and some frequency of micturition, but no pain; tubercle bacilli were found in the urine. There was also a discharging sinus from a tuberculous focus in the sternum of some four months' duration. The patient was a healthy-looking man, though he had lost weight. He has now had weekly injections for three months and is still under treatment. Tubercle bacilli are still present, but his general health has improved remarkably and he has put on nearly a stone in weight. The focus in the sternum has apparently completely healed. The ureters were not catheterized on account of the orifices being obscured by general cystitis.

CASE IV.

A girl, aged 19, with very advanced renal and bladder tuberculosis. After treatment for a few weeks without benefit it was realized that the case was quite hopeless; the patient died very soon after.

Many cases of bone and gland tuberculosis have been treated by this method, but as in all these cases other methods of treatment, local and general, have been employed at the same time, details of particular cases do not carry much weight. One such case may, however, be worth mentioning.

CASE V.

A boy, aged 13, had tuberculous lesions in a metatarsal bone in each foot; skiagrams showed evidence of bone disease, a focus in the fleshy part of the nasal septum, and a swelling, apparently tuberculous, in the left wrist. The diagnosis was made only on clinical grounds and on skiagraphic appearances. Local treatment consisted only of immobilization of the wrist, and he was kept entirely off his feet. He has had treatment by injections for four months; a very striking improvement in general health, with increase in weight, was seen soon after the treatment was begun, and the local lesions are now nearly healed, though there is still slight discharge from the bone foci and a dry granulating area on the septum, which will probably require local treatment. He was treated as an out-patient.

Non-tuberculous Infections.

The following are cases of non-tuberculous infections treated by this method.

CASE VI.

A male, aged 18, with persistent pyrexia and metastatic abscesses following operation for suppurative appendicitis. For a month after operation temperatures varying from 101° to 104° were recorded daily, and several metastatic abscesses were opened. After the second injection definite improvement was observed, the temperature rising only once to 101°; the third injection was followed by almost normal temperature, 100° being recorded once. Six injections were given, the temperature remaining normal after the fourth. At the same time the improvement in the general condition was most striking, and the abdominal wound, previously sluggish and discharging, healed rapidly. The injections were given every four days.

CASE VII.

A female child, aged 5, was admitted with empyema; she was suffering also from pyelitis (*B. coli*), and had a mitral systolic bruit, apparently organic. After thoracotomy and drainage the temperature still remained irregular, and a second collection of pus in the chest was drained without effect on it. A month after the operation the child was very gravely ill, the temperature being 103° to 104° daily. After the second injection (three days' interval) a striking fall in the temperature was observed, and, except for a sudden rise to 103° for a few hours a week later, the chart remained almost normal for a month, and a very material improvement in general health coincided with the disappearance of the pyrexia. As the temperature again became irregular for a few days, two more injections (0.5 c.cm.) were given, with the same result as before. Some pus cells still remained in the urine when the patient was discharged.

These are examples of cases treated on the surgical side, but it must be acknowledged that there have been failures: a case of pulmonary infection after operation for perforated gastric ulcer and a case of actinomycosis, among others, were not benefited in any way. Also some cases of multiple sinuses from bone necrosis of very long standing, which I have been allowed to treat by the courtesy of the officer in charge of the Pensions Hospital, Leicester, have not shown any material improvement. By the courtesy of my medical colleagues I have treated a few medical cases.

CASE VIII.—*Persistent Urticaria.*

A man, aged 27, had suffered since 1917 from troublesome urticaria affecting the skin of the limbs and face, and quite uninfluenced by treatment. It had appeared during military service, and he was drawing a pension for it. After seven injections (weekly intervals) the attacks had ceased, and had not recurred several months after, since when I have lost sight of him.

A case of "urticaria dermatographica" was not influenced by a course of injections.

CASE IX.—*Pulmonary Tuberculosis.*

A man, aged 56, whose general condition was fairly good, presented evident signs in the lungs and tubercle bacilli in the sputum. For some reason he had refused to remain in a sanatorium for more than a few weeks. After treatment by injections for four months no tubercle bacilli were found in the sputum after two examinations, and his general health had improved.

Though this case is mentioned I do not, of course, claim that this method of treatment is applicable to pulmonary tuberculosis, though on general grounds it might be considered to be worthy of a more extended trial.

My hope that general paralysis might reasonably be expected to be favourably affected by this method of treatment was based on the now well known results of treating general paralysis by infecting the patient with the malaria parasite. I suggest that this "treatment by malaria" really amounts to a periodical intravenous injection of destroyed cells, and that the beneficial effects are due to an immunizing reaction against this cellular toxin in the way that I have described. A patient was referred to me as being, clinically, quite definitely a case of general paralysis, though no Wassermann test had been done (he was not a hospital patient). After eight injections the improvement in mental and general condition was quite definite, and, I am told, has been maintained, though partial lack of bladder control remains.

HELIO THERAPY.

I believe there are strong grounds for regarding heliotherapy, as carried out with such success by Professor Rollier in Switzerland and Sir Henry Gauvain in Hampshire, as being really a method of application of the "treatment by immunization." I suggest that the mode of action of heliotherapy is briefly as follows: (1) Although it has not been proved that the tubercle bacillus has a haemolytic property, like many other pathogenic bacteria, it is probable that the pyrexia, anaemia, and debility are due, in part, to the endocellular toxin. The natural defensive powers of the body are capable, up to a point, of dealing with the tubercle bacillus, but are handicapped by the action of this toxin. (2) The sun's rays destroy a certain number of red cells in the superficial capillaries, probably first destroying the endothelial cells forming the capillaries. (The bronzing of the skin may be evidence of blood destruction, but this is uncertain; it is well known that those patients do well whose skin bronzes readily.) (3) The destruction of red cells in the skin sets free a small amount of the endocellular

toxin which acts as an immunizing agent, being favourably placed for acting in this way.

The process of exposure to the sun must be gradual or a dangerous reaction may be set up; the explanation of this is, I think, that the destruction of a large number of cells, before immunity to the toxin has been set up, results in the formation of an excess of the same toxin that is already producing the symptoms of the disease, in the same way that an overdose of a vaccine is followed by a severe reaction.

It is impossible to believe that the rays of the sun can have such powers of penetration as to have any direct bactericidal effect on tubercle bacilli deeply situated in a gland or bone. The explanation that I have suggested seems to me to be more probable, and certainly more tangible, than that given by Dr. Rosselet in Professor Rollier's book on heliotherapy:

"The energy given out by the radiations is stored and carried in the blood stream to every part of the body; when liberated it stimulates the intracellular processes of oxidation and reduction."

In this connexion it is of particular interest to note that guinea-pigs inoculated with haematoporphyrin acquire an extraordinary hypersensitiveness to sunlight and ultra-violet rays. I do not know what explanation of the phenomenon has been given, but I believe that it may be regarded as an anaphylactic reaction, the haematoporphyrin (a derivative of red blood cells) sensitizing these animals so that a subsequent dose of a similar or closely allied substance, liberated by the destructive action of sunlight on red cells, rapidly produces toxic symptoms.

SUMMARY.

It is well known that the red corpuscles of animals of one species are toxic to animals of another species; Vedder⁶ has shown that human red-cell stroma, freed from haemoglobin, is exceedingly toxic to rabbits. In this communication an attempt has been made to show that the stroma of human red cells, when disintegrated by heat or by mechanical means, is toxic to the individual from whom the blood was withdrawn and to other individuals; it is also shown that many bacteria have a disintegrative effect on red cells. It is inferred therefrom that this endocellular toxin is a factor in causing the manifestations of bacterial infections, and a method of treatment is suggested based on these deductions and aiming at immunizing the body against this toxin.

The toxin produced by the destruction of red cells is probably an example of a "poison of metabolic origin," such as gastrototoxin, hepatotoxin, etc., though in most cases these toxins have been produced by the injection of the particular cells of one animal into another of a different species. C. Bolton⁷ produced an isogastrototoxin by immunizing the rabbit with the gastric cells of a rabbit, and Ehrlich⁸ has shown that an isohaemolysin might be formed in the goat by the injection of goat's blood which would dissolve the blood of another goat. I am not aware that it has been previously shown that human disintegrated red cells are toxic to the same and other individuals.

Reference must be made to a paper by S. G. Billington,⁹ in which he describes how certain "coccoid bodies" are formed from the red cells when a few drops of blood are added to a tube of distilled water with 0.5 per cent. ammonium carbonate and heated to 58° C. These coccoid bodies he regards as possibly allied to or identical with micro-organisms, and he has treated a large number of bacterial infections with vaccines prepared from these bodies. I have found that the debris resulting from heating washed red cells in the way I have described consists, microscopically, of similar "coccoid bodies"; if the medium is normal saline the spheres are large—about a quarter the size of red cells—while if weaker saline, or distilled water, is used they are smaller and have the appearance and often the arrangement (pairs, short chains, etc.) of cocci. Their staining reactions, however, are these red cells.

REFERENCES.

- ¹ Adams's *Pathology*, vol. i, p. 309. ² Wade Brown: *Journ. Exper. Med.*, 1912, p. 538. ³ E. Ponder: *Erythrocyte and the Simple Haemolysins*, Oliver and Boyd, 1924, p. 136. ⁴ C. J. Bond: *BRITISH MEDICAL JOURNAL*, January 11th, 1919. ⁵ Idem: *The Leucocyte in Health and Disease*, Lewis and Co., London, 1924. ⁶ Vedder: *Journ. of Immunol.*, 1919, p. 143. ⁷ C. Bolton: *Ulcer of the Stomach*, p. 65. ⁸ Ehrlich: *Berl. klin. Woch.*, 1900, No. 21 (quoted from Bolton, *Ulcer of the Stomach*). ⁹ S. G. Billington: *Lancet*, March 1st, 1924.

SOME NOTES ON EPIDEMIC ENCEPHALITIS.*

BY

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It is not my intention to attempt to give anything like a complete account of the cases of epidemic encephalitis admitted to the fever hospitals under my care during the very sudden and extensive epidemic in Belfast during the spring and early summer of 1924. I shall merely endeavour to refer to some of the outstanding features of that outbreak, and to give some notes and figures gleaned from my experience of that very large number of cases.

The outbreak began at the end of March, 1924. For the first three weeks the cases were few; about the middle of April there was a sudden large increase in admissions, and cases continued to come in large numbers until the end of June, when the epidemic ceased even more suddenly than it began. This seasonal outbreak coincides exactly with our experience in 1920, the only other year in which there has been any extensive epidemic in Belfast. The total number of cases admitted to the fever hospitals in the outbreak of 1924 was 183.

Differences in the type of attack in the cases in this recent outbreak, compared with the earlier epidemics, have been noted everywhere, but I think much, though not all, of this difference is more apparent than real. The descriptions of the signs and symptoms in the early stages of the disease which have appeared in medical literature are necessarily to a large extent based on observations made on cases after their admission to hospital. Whereas in the earlier outbreaks cases very rarely reached the hospitals until lethargic symptoms had developed, in this epidemic the cases were much more quickly diagnosed, and were frequently sent to hospital in the stage of excitement and insomnia. This naturally left with the hospital physicians a very different picture of the early signs. I know that, speaking for myself, I did not fully recognize until the outbreak of 1924 the very great diagnostic value of a history of persistent insomnia, mental excitement, and talkativeness at the onset.

SYMPTOMS.

The prominent symptoms at the onset of this outbreak were: (1) Fleeting superficial neuralgic pains; (2) nocturnal insomnia, often complete and lasting for several nights; (3) mental excitement and exaltation, great restlessness and talkativeness; a little later came (4) diplopia and other eye signs; (5) muscular twitchings of varying degree; (6) delirium of varying degree; and later still (7) lethargy of varying degree. It is, of course, true that in many cases some of these symptoms were entirely absent.

1. *Neuralgic pains* were reported in the large majority. Common sites were: the scalp; over the ears and sides of neck, often extending over the shoulder and arm; the forearm; the fingers, especially the thumb; over the iliac crests, one or both; occasionally pains in the leg or foot were present at the onset, but more commonly this was a later, and often very troublesome, manifestation. In a few cases the first symptom was pain high up in the axillae, and in some very acute pain in the perineum. In many cases if the painful part were firmly handled the pain was slight or absent, but light touching or stroking was intensely painful.

2. *Nocturnal insomnia* was present in a large majority as a very early sign. Many patients were unable to sleep at all for four, six, or even eight nights.

3. *Mental excitement, restlessness, and talkativeness* were very common at the onset; the talkativeness was particularly striking in many cases seen in the very early stage. In many there was a history that if left alone the patient whistled or sang all through the night; and more than one patient after admission to hospital treated the ward to a continuous vocal concert throughout the night.

* Abstract of a paper read before the Ulster Medical Society on