to the occurrence of secondary sclerosis in the pulmonary artery, but I think that this explanation can only occasionally be the correct one, possibly only in exceptional cases." (Owing, however, to obstruction in the circulation of blood through the lungs in these cases, there is increased blood pressure in the pulmonary artery, as confirmed by the presence of dilatation and hypertrophy of the right side of the heart, and therefore degenerative changes in the pulmonary artery, it must be admitted, are very likely to occur.) I also mentioned that, so far as I could judge, the best marked polycythaemic reactions occurred in individuals (especially asthmatics*) of Jewish race, and at about middle age, when the reactive power in the haemopoietic bone marrow is probably stronger than in old age. A feature of some diagnostic importance in these cases is that the cyanosis and erythrocytosis may exist for a long period before the patient's death.

Dr. Arrillaga, who read the French translation of my paper (1913), kindly wrote to me (in April, 1913) and sent me a copy of his elaborate medical thesis (National University of Buenos Aires, 1912) entitled "Esclerosis secundaria de la arteria pulmonar y su cuadro clinico (*cardiacos negros*)."

He wrote to me that my cases were examples (several of them certainly were) of so-called "black cardiac cases"—"cardiacos negros"—the clinical and pathological condition of which has been described in a clinical lecture, delivered in 1901, by Professor Abel Ayerza (whose pupil he was), of the National University of Buenos Aires; he especially drew my attention to the changes which had been found in the pulmonary artery.

The term "Ayerza's disease" for this group, "cardiacos negros," seems to have been first used in a medical thesis by Dr. C. A. Marty on "La tension arterial en la tuberculosis pulmonar" (Buenos Aires, 1909, p. 45), in which (according to A. S. Warthin—see further on) the author says that there is a special group of cases worthy of attention because of increased pulmonary artery tension associated with hypertrophy of the right heart, pulmonary arterio-sclerosis, and chronic cyanosis, described eight years previously by Ayerza as "cardiacos negros." According to Warthin (see further on), the term "Ayerza's disease" has also been used by Escudero and Garcia del Real, and in 1917 Barlaro (*Rev. Assoc. Argent.*, 1917, vol. xxvi, p. 121) reported a case of "Ayerza's disease" characterized by extreme cyanosis, asthma, intense dyspnoea, cardiac hypertrophy, polycythaemia rubra (an erythrocyte count of 6,600,000), enlargement of the liver, but no palpable enlargement of the spleen, a positive Wassermann reaction, and pulmonary arterio-sclerosis. A. S. Warthin's case was described at the thirty-fourth annual meeting of the Association of American Physicians in June, 1919,¹⁰ as "a case of Ayerza's disease—chronic cyanosis, dyspnoea, and erythraemia, associated with syphilitic arterio-sclerosis of the pulmonary arteries." The patient was a labourer, aged probably about 43 years. At the end he became very somnolent (I suppose from chronic carbonic acid poisoning). The necropsy showed (amongst the other findings) typical mesarteritis of the pulmonary artery and aorta (microscopical examination), fibrosis and emphysema of the lungs, and extreme dilatation of the right heart. I should regard the so-called erythraemia in Warthin's case as an example of chronic cyanosis, with secondary polycythaemia rubra of "cardio-pulmonary" origin, on an old syphilitic basis. I do not believe that syphilis is an essential factor in "cardiacos negros," and do not think it was present in most of my own cases. I think, moreover, that the word "erythrocytosis" (that is, secondary polycythaemia rubra) should be used instead of "erythraemia," because the polycythaemia rubra is obviously secondary and of "cardio-pulmonary" origin.

The cases are probably not likely to be often confused with typical erythraemia ("Vaquez's disease"). Nevertheless W. S. Lucas, in his elaborate and excellent paper of 1912,¹¹ has, I think, described two typical cases (the two original reports in his paper) of secondary polycythaemia rubra of cardio-pulmonary origin (without splenomegaly), that is to say, *cardiacos negros* of Ayerza, as examples of erythraemia. It is not therefore surprising that Warthin, who refers to Lucas's extensive survey of the subject of erythraemia, regarded cases of "cardiacos negros" or "Ayerza's syndrome" as examples of cases that had been included under the heading "erythraemia."

Clinically, the obvious signs of disorder of the respiratory system (and the clubbed fingers when present), the usual absence of evidence of splenic enlargement to ordinary palpation, and the very frequent presence of an enlarged liver (chronic passive congestion), should greatly help to differentiate Ayerza's syndrome from cases of true erythraemia.

5. *Secondary Polycythaemia Rubra connected with Congenital or Acquired Heart Disease.*—These cases are so well known and of such common occurrence that I need scarcely mention them. The cyanotic condition of the blood, due chiefly to stasis, is the main factor in exciting the erythrocytosis. The spleen is seldom palpable to ordinary clinical examination.

I have now shortly discussed the main groups of

secondary polycythaemia rubra which should always be kept in mind in regard to the diagnosis of erythraemia. There are certainly other varieties of erythrocytosis (accompanied or not by enlargement of the spleen), which might be considered in a longer survey of the subject. Another paper could be devoted to the consideration of: (1) The temporary moderate polycythaemia rubra occasionally connected with tuberculosis, especially tuberculosis of lymphatic glands in young adults, with or without slight splenomegaly; (2) a form of "plethoric obesity" with endocrine disturbance, especially in women with positive Wassermann reaction, about the menopause period; (3) temporary polycythaemia rubra in children with inherited syphilis and with more or less splenomegaly, and in some rachitic children with or without splenomegaly.

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THE ACTION OF CHEMIOOTHERAPY.*

BY

J. E. R. McDONAGH, F.R.C.S.

Resistance.

To understand the action of chemotherapy in the body it is necessary to bear in mind that the parasite is attacked indirectly through the host's resisting substance, and not directly by the drug prescribed. The resisting substance is the protein in the serum and the protein which forms the protoplasm of such cells as lymphocytes and their offspring, the plasma cells. The action of the former is general, and of the latter local. The protein exists in the form of particles, which can be best visualized by calling to mind the picture produced when the sun enters a darkened room through a crevice in the blind and shows up the dust as minute motile particles. In the case of the serum the particles move about in a liquid medium, and not only is there a constant interchange between the solution itself and the particles suspended therein, but there is also a rigid balance maintained between the two, known as the normal hydrogen-ion concentration. Any disturbance of the normal hydrogen-ion concentration prevents the particles from fulfilling their functions. If we compare each particle with a man we shall be able to picture its action. A man is a complex machine moving and living, provided he has sufficient oxygen around him. There must be a balance between him and the air, if he is to do his work—the normal hydrogen-ion concentration of the protein particle. When our man is attacked by another man—the parasite—he will endeavour to overcome him by adjusting things around him and by calling others to his assistance, if the intruder has not been vanquished in the first onslaught. The same with the protein particle: it is ever ready to resist invasion unless its oxygen supply has been lessened by such substances as alcohol, etc.—hence the reason why a patient under the influence of alcohol is more likely than one sober to contract a venereal disease. Should the parasite win its first encounter and become implanted in the host, it has to guard its own oxygen supply very jealously, as it and its comrades are far outnumbered by the protein particles, which by this time have called others to their assistance. The fight between the parasites and the protein particles can be compared with trench warfare, as the fight is a surface one with an interspace between,

* There is a neurotic element probably present in some cases, which may be increased by mental worry, or also, it is just possible, by the habit of "coitus interruptus," to which habit one of my patients, a strongly built man (a joiner by trade), aged 39 years, was inclined to attribute the causation of the "shortness of breath" from which he commenced to suffer at about the age of 29 years.

* A paper read before the Suffolk Branch of the British Medical Association, June 17th, 1920.

like no-man's-land, and the fight is one of electrical neutralization, which corresponds to the arms of human combatants. The parasite exhibits on its surface not the oxygen necessary for its existence, but the means whereby this supply of oxygen is maintained. The host's protein particles, on the other hand, exhibit their oxygen on the surface, as there is not the same need to conserve it. As the oxygen on the surface of the protein particles electrically neutralizes the hydrogen which maintains the supply of the parasites' oxygen, then, provided sufficient of this oxygen is to hand, the parasites' means of living will be cut off and they will perish. This is the warfare practised in all parasitic invasions, but is only successful, generally speaking, from the host's point of view, in staphylococcal and streptococcal infections. As parasites became more advanced, they protected themselves by forming impregnable capsules and spores, while others have entered the cells of the host they were attacking, which have rendered them wellnigh invulnerable. The cancer parasite, which I take to be the host's cell itself, so physically altered as to become parasitic on its surrounding fellow creatures, has so far resisted all attempts to overcome it. The protein particles have advanced also in their methods of attack by increasing in number and size, and by building up their structure to approach as near as possible to that possessed by the parasite. These manoeuvres not only enable more of the drug prescribed to be taken up by the particles, but they intensify the surface action between the parasites and themselves, just as two pieces of wood will fit better when dovetailed than when merely placed side by side. Should none of these efforts suffice to vanquish the parasites, and should the particles have spent themselves in forming their surface oxygen by the usual methods, they are obliged to resort to indirect methods to produce this oxygen, and this they do by calling into play their reducing action. It is the reducing action which prevails on the surface of the parasites and which conserves their oxygen beneath; therefore when the host's protein particles call upon their reducing action—the circumstance which marks the chronic stage of an infection—they themselves approach to the conditions under which the parasites are living. If the fight be mainly local, what has taken place in the protein particles of the serum takes place in the attacking cells. Should such cells still be unable to overcome the enemy, they are liable to undergo changes (nuclear division and nucleolar activity) in which the nucleoli, by division and budding, attempt to achieve what the cells themselves have failed to do. These changes destroy the relationship between such cells and those surrounding them as to make the former parasitic, and this is the way in which I think that chronic inflammation may lead to malignant disease. Therefore, in attempting to overcome an infection, the attacking cells may themselves become parasitic.

Oxidation and Reduction.

We must now discuss the maintenance and increase of the oxygen on the surface of the protein particles. The surface active oxygen, which appears most likely to be a modified hydroxyl group, with a negative electric charge, is maintained in the human body by the action of iron. In certain invertebrates copper fulfills this purpose, and in plants manganese. The metal acts as a catalyst—that is, it can produce an enormous amount of active oxygen without itself being used up in the process, but it requires a medium to work upon before its work is done, and success is not achieved in every case, partly because this medium is destroyed in the process. Most metals act as oxidizing agents, though with varying degrees of activity, but as most of them are particularly apt to destroy the medium just mentioned, toxic manifestations are liable to follow their use. The medium is formed in the reducing action—an action regulated in all plant and animal life by sulphur, a non-metal, and enhanced by iodine. Just as a metal forms oxygen in the form of hydroxyl, sulphur forms hydrogen which possesses a positive electric charge. The action of this hydrogen is to convert the metallic compound formed in the oxidase reaction back into the form in which it acts as a catalyst. Hence destruction of the hydrogen on the surface of the parasites by the hydroxyl group on the surface of the protein particles by electrical neutralization robs the parasites of their means of keeping up the active oxygen necessary for their

existence. It will now be clear from these few sentences why metals are indicated before non-metals in the acute stage of an infection, and non-metals before metals in the chronic stage, why in *both* stages both metals and non-metals have their right place, and why a metal is an antidote for non-metallic poisoning, and a non-metal for metallic poisoning.

Chemiotherapy.

We now come to discuss the choice of the element and the form in which it should best exist. Iron was one of the commonest metals which was found on the earth's crust when the ball of elements in the gaseous state had condensed on the surface so far as to render life possible. As iron has two hydroxides which are readily reversed by hydrogen, it is not to be wondered at that cellular activity was largely bound up with the metal iron, and that iron is the metal to-day which regulates the oxidizing action of our protein particles. The only other metal exactly akin to iron is manganese, hence my reason for having introduced this metal for the treatment of acute coccal infections. The action of a metal depends upon the amount which the protein particles can take up. The particles can take up little or none if the metal is incorporated in the form of a simple salt; it can take up much if in the simple colloidal form, and more still if the molecule be so increased in size and form as to approach that of the protein particle itself, just as the surface action between the protein particles and the parasites is increased as the former build up their molecules to simulate those of the latter. This is called an homologous stereo-chemical molecular configuration, and it is the cause of specificity. As the number of protein particles produced bears a ratio to the kind and severity of the infection—being few if the parasite is lowly developed and numerous if it is highly developed—it can readily be understood that the state in which the metal is needs to be more complex in protozoal infections than in bacterial infections. As the response on the part of the host is less the more lowly the organism, and as metals, if used in too large doses and too frequently, destroy the patient's protective substance, it becomes clear why simpler products should be used in bacterial than in protozoal infections, and why in all cases, especially in the former, so much attention should be given to the dose and frequency with which the injection is prescribed. In acute staphylococcal and streptococcal infections colloidal manganese, now supplied in the form of trimine, has produced results which far exceeded my expectations; but not more than three injections should be given at a time, and it is rarely necessary to exceed a dose of 2.0 c.cm. Trimine contains iron and zinc in addition to manganese; my reason for making this change was because I found that three injections of three different oxidizing agents gave better results than three injections of any one. When we come to gonorrhoea, we find that trimine is useful, especially in the acute stage of complications, such as periurethral abscess, cowperitis, prostatic abscess, and epididymitis, but not generally so efficacious as in the simple coccal infections. This is due, in my opinion, to the fact that the gonococci quickly take on an intracellular habitat, and live at the expense of the polymorphonuclear leucocytes, not vice versa as is usually thought to be the case. I take phagocytosis to be a laboratory phenomenon, and not one which occurs *in vivo*. The function of the polymorphonuclear leucocytes is to remove from the battlefield the bodies of organisms which have been killed in the way already described.

As gonorrhoea is a disease which is so likely to be contracted if the patient is under the influence of alcohol, owing to the effect alcohol has in depressing the oxidizing action of the protein particles, I introduced colloidal palladium for use in the acute stage of a first infection, with excellent results in those cases which are caught early enough. Palladium was chosen in view of its extraordinary power in temporarily occluding several thousand times its own volume of hydrogen—an action which might naturally be expected to increase for a time the oxidizing effect of the protein particles. The gonococcus is the organism *par excellence* for giving rise to the formation of fibrous tissue. Fibrous tissue formation is a sign that the infection has reached the chronic stage, and often—to use a loose term—that the blood is too acid. As this synchronizes with an increased reducing action

of the protein particles, and as in the chronic stage of an infection relatively more of the drug prescribed has to be taken up before the effect desired is produced, it became necessary to have a preparation of a non-metal with as large a molecule as possible, so as to enable the protein particles to take up the maximum quantity of the element. For this purpose I introduced intramine, which is an amino-compound of sulphur. Intramine has given results in gonorrhoeal rheumatism and in the chronic stage of gonococcal complications which can be achieved by no other preparation in use at present, and it is many times more powerful than plain colloidal sulphur, just as arseno-benzene is infinitely superior to plain colloidal arsenic. Iodine acts by increasing the sulphur metabolism, owing to the effect it has in converting a substance (mercaptan) formed in the reducing action back into catalytic sulphur. In other words, iodine doubles the action of sulphur, and acts in the reductase reaction as does hydrogen in the oxidase reaction. Owing to the disadvantages of the salts of iodine and to the inefficacy of most of the organic preparations, I introduced colloidal iodine, which can be injected intravenously in the same form as it is taken internally without ever producing symptoms of iodism. There being no specific action in my oxidation and reduction theory of chemotherapy, it will be clear why intramine should be so valuable in the chronic stage of all infections, in the late stages of syphilis, in metallic and other acid intoxications, and applied locally to indolent and chronic sores. In mercurial and arsenical poisoning the combination of colloidal iodine and intramine will cause almost instantaneous amelioration, and it has already saved many lives. The use of intramine in early syphilis rids primary sores of their induration and diminishes the incidence of neuro-recurrences, while in certain forms of late syphilis—glossitis, for instance—intramine will frequently achieve what arseno-benzene has failed to do. The reason why arsenic was chosen for the basis of chemotherapy was because it is one of the easiest metals to work with; it has no specific action, and I am sure if suitable organic compounds of iron and manganese could be produced, no more arsenic would be employed, and we should be saved the hundreds of cases of arsenical poisoning which are occurring, and the enormous increase of nervous syphilis would be reduced to a minimum. The reason why arseno-benzene appears to be so efficacious in syphilis is merely because there are more protein particles formed in this than in any other disease, consequently large amounts of a drug can be taken up, and the oxidizing action of the protein particles can be increased to the maximum. Mercury acts in syphilis in the way it does, first, because of the increased number and size of the protein particles in this disease, and secondly, because in virtue of its high atomic weight it has the properties approaching those of a colloid, and is therefore readily taken up by the protein particles. Any metal having as high an atomic weight or higher will produce the effect on a syphilitic lesion which mercury does; thorium will, for instance. This is probably the reason why the emanations of radium, which have a high atomic weight, are useful in malignant disease. In treatment with metals and non-metals, destroying the patient's resistance, which is so easily done by using too large doses and prescribing too many injections, will give the parasites the upper hand, hence the reason why we are seeing so many cases of syphilis to-day which seem to get worse the more arseno-benzene and mercury is given, and cases which relapse even while under treatment. Unfortunately the disappearance of symptoms does not mean cure of the disease, and all we can really say we do by treatment is to render organisms dormant by increasing the resistance of the host which is harbouring them. Consequently we should in treatment think of the patient and not of the disease, so as to avoid destroying his resistance, which is so easily done by over-treatment. Ideal chemotherapy, then, is to render organisms dormant and keep the host's resistance in a state which will maintain them so.

It is estimated that from October, 1918, to March, 1919, 2 per cent. of the American aborigines died of influenza. In some districts the mortality amounted to 41.2 per 1,000.

A COMMITTEE has been formed to erect a marble monument at Tournai in honour of the eighteenth century ophthalmologist, Michel Brisseau, well known for his work on cataract.

THE EFFECTS OF THE EMOTIONS ON GASTRIC SECRETION AND MOTILITY IN THE HUMAN BEING.

BY

T. IZOD BENNETT, M.D., M.R.C.P.,

ASSISTANT PHYSICIAN, MIDDLESEX HOSPITAL; LATE MEDICAL ASSISTANT AND DEMONSTRATOR OF PHYSIOLOGY, GUY'S HOSPITAL;

AND

J. F. VENABLES, M.B., B.Ch.,

CHIEF ASSISTANT, NEUROLOGICAL DEPARTMENT, GUY'S HOSPITAL.

DURING the past year the fractional method of gastric analysis, first introduced by Rehfuess in the United States, has been employed by one of us (T. I. B.) in conjunction with Dr. J. A. Ryle, in an extensive investigation into the secretion and motility of the gastro-intestinal tract in health and disease. The wide possibilities which the method offers for physiological research were soon apparent, and the present communication is a preliminary report concerning one branch of the inquiry.

That the emotions can moderate digestion to a notable degree has long been recognized; the work of Cannon on frightened animals, and Pavlov's observations on appetite juice are the best known examples. But the present is, we believe, the first occasion on which these effects have been demonstrated on the human subject, and we hope that this communication may lead others to continue an inquiry which, owing to the method employed, allows accurate data to be collected concerning emotions which cannot be evoked in mere animal experiments.

The Method.

The subjects of our experiments were all healthy medical students from the Physiological Department of Guy's Hospital. All experiments were carried out in the morning, beginning at 9.30 o'clock, the subject having taken nothing by the mouth since the previous evening.

In each subject the normal curve was first ascertained; a gruel meal was given, made by boiling two tablespoons of oatmeal in a quart of water until the bulk was reduced to one pint and then filtering through muslin. Samples of the gastric contents were then withdrawn every quarter of an hour through the Rehfuess tube, and the percentage of free and total acid estimated and plotted in a curve. Careful histories were taken from all cases in order to ascertain the most suitable emotive disturbance to be evoked. Each subject was several times interviewed and a light degree of hypnosis produced before the final experiment. The subject's normal curve and emptying rate being established (the latter by finding, by means of iodine, the point at which starch disappeared from the samples of gastric contents), he was told to come up, again without food or drink, on a subsequent morning. On arrival the Rehfuess tube was swallowed and the gruel meal given, the first few specimens were drawn off at the usual times and the subject was then hypnotized. One of us (J. F. V.) then made suggestions appropriate to evoke the required emotion, whilst the other continued to withdraw gastric samples at the regular intervals. Hypnosis was never continued for more than half an hour, nor was it ever pressed to a deep degree. The subjects were always able to remember everything that had happened and had been suggested to them, but were never informed before the experiment as to what emotion was going to be suggested.

It is not possible at the present time to give any precise definition of the hypnotic state; at the depths to which it was carried in our experiments it is very closely analogous to light sleep; the subject has cut off his sensory receptive system from all external stimuli, save those reaching him, via his ears, from the observer. His voluntary musculature receives no efferent impulses from his brain, which for the time being concerns itself solely with the transmission of those reflex and involuntary impulses which result from the suggestions of the observer.

After the hypnosis, on waking up, the subject passed the remainder of the morning in a manner as similar as possible to that of the previous control mornings—that is, he read a newspaper or a textbook, talked with his companions on indifferent topics, or helped with the gastric analyses. Specimens of his gastric contents were still withdrawn every quarter of an hour, until the stomach was empty. In this manner two curves were obtained, the first being the normal curve for the individual, the second a curve showing the effects of the suggested emotion. The emptying rate was also carefully recorded in each case.

Results.

1. *Nausea*.—The subject selected for this experiment was a healthy man of athletic type; for experimental