product is such that the effect is superadded to that exerted by the specific products of the disease germ we have a summative action, the infective power of the pathogenic organism being increased; while if on the other hand the action exerted by the sterile bacterial products on the cells of the animal tends to antagonise that exerted by the specific disease germ, we have a dissipative action, the process of infection being rendered less acute or even abortive. How very complicated this interaction of the toxins on the cells of the animal may be is indicated where a rabbit is subjected to a mixed infection of anthrax and erysipelas. The animal frequently recovers from the anthrax infection which would otherwise have been fatal, but it has sometimes been observed that the animal succumbs to the erysipelas, no trace of anthrax being obtainable, although the streptococcus would not by itself be fatal to these animals. This would seem to indicate that while the products of the streptococcus tend to antagonise the effects of the anthrax, the effect of the latter toxin may be superadded to those of the streptococcus. It must be recognised accordingly that the action is a specific one, and that we must search for that special toxin which exerts this cumulative action in the case of each specific disease germ.

Guided by this fact that animals can be rendered more susceptible to infections to which they are normally subject, I have been experimenting to ascertain whether it might not be possible to render animals susceptible to infections to which they are normally refractory. That the principle is in all probability correct was indicated in my last report,¹ where I stated that animals could be infected with gonococcus material in such a way that a purulent discharge of the urethra can be set up, which endures for several weeks. The examination of this discharge indicated the presence of many pus organisms along with apparently the gonococcus. Since the products of *M. prodigiosus* and other toxins undoubtedly aid the process of infection with pus-producing organisms to which this animal is not normally very prone, it may perhaps be questioned if the same effect could be produced with a pure culture of the gonococcus. It must be remembered, however, that the profuse urethral discharge in the human subject seems to be invariably accompanied by the presence of these pus organisms, to which the pus formation is no doubt in great part to be ascribed. This very encouraging result led me to experiment in the same direction with vaccine material. The cultures and sterile products of *Bacillus prodigiosus*, *Bacillus tuberculosis* (tuberculin), *Bacillus malleus* (mallein), *Bacillus diphtheriae*, and other organisms have been used alone and in conjunction to attain this end. The results obtained, although indicating clearly an increased susceptibility of the animal to the infection, have not up to the present been of such a definite character as to permit of their yet being used for experimental purposes. Thus when we inoculate with vaccine material the mucous membrane of the upper eyelid of an animal, under the influence of other toxins, we frequently have distinct inflammation even with the production of ulceration, which may after a considerable time become very marked, due, however, in great part probably to the constant irritation of friction due to the movement of the eye. The primary lesion, however, is not so definite or so certain that much reliance could be placed on it as regards the question as to whether the inoculation of vaccine material had "taken" or failed. The effects of inoculation varied at different times, and it would appear that the best results were obtained with fresh material introduced in considerable quantity. These results, I think, indicate only that I have not yet discovered the special product which would exert its cumulative influence on the infection of vaccinia, and I hope to continue the investigation on these lines by experimenting with other substances.

Recent advances in our knowledge have rendered it probable that normally refractory animals may be rendered susceptible to infection by another method. It has been found by Roux and others that the vaccination of an animal with one disease may render it very much more susceptible to the toxin of another organism, and similar suggestive results have been obtained in other departments of bacteriology. It would appear, indeed, as if the constitution of an animal can be so altered by vaccination to a certain disease that it will react to

another disease like an animal of a different species. I have not yet, however, had an opportunity of extending the research in this direction.

The influence of local conditions in aiding infection have been observed chiefly when substances have been introduced into the tissues which apparently exerted a devitalising influence on the cells. That this is the most probable reason is shown by the fact that physical injury to the fixed cells, such as a bruise produced by a blow, will produce the same effect in aiding infection. If this explanation holds good, any means which abrogated the action of the living tissues locally ought to exert a similar influence; thus, if the germ were inoculated into a sponge which was introduced under the skin it should be able more readily to induce infection, and this I have found as a matter of fact is really the case. Unfortunately if other organisms obtain an entrance at the same time they are also able to multiply undisturbed and complicate the process by inducing a mixed infection. To avoid this disadvantage of the method (the entrance of foreign organisms) I have obtained the same result in a different way; a solution of sterile colloidal silica, prepared in the same way as Winogradsky recommended for the cultivation of his nitrifying organism, can be injected subcutaneously, and this becoming solid *in situ* on mixing with the animal fluids, provides a pervious sterile foreign body, in which the organism can multiply undisturbed by the surrounding tissues. It was observed in some cases that its action was not so marked as that exerted by the sponge, and this appeared to be due to the contractile force of the skin and tissues tending to compress the jelly into a very small compass. This difficulty was obviated, however, by making the injection into a loose fold of skin. The method of infection I now use is as follows: A sufficient quantity of a broth cultivation of the organism experimented with is injected subcutaneously, and, without removing the needle from the skin, the syringe is refilled with the colloidal silica, which is then at once injected. On the death of the animal a portion of the gelatinous silica can be introduced into a tube of broth, and this fluid used for inoculation of the second animal, a series of transmissions being thus carried out without risk of outside infection. This is an exceedingly effective and convenient method for increasing the virulence of pathogenic organisms, and should find useful application in the production of those virulent cultures which are requisite at present for the production of curative serums. It can, of course, be combined where necessary with the constitutional methods which tend to favour infection. This method, of course, could not be made use of until the organism experimented with had been obtained in a pure form, and therefore could not be utilised at present in my research.

REPORT ON THE EXCHANGE OF BLOOD GASES IN BRAIN AND MUSCLE DURING STATES OF REST AND ACTIVITY.

BY

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INTRODUCTORY.

Four years ago, in his Croonian Lecture at the Royal Society, A. Mosso¹ adduced evidence to show that the brain is a seat of active combustion. By a long series of thermometric observations, he has come to the conclusion² that the temperature of the brain is frequently higher than that of the rectum or even of aortic blood, and, moreover, that the temperature of the brain rises still higher when that organ is thrown into activity by direct stimulation or by drugs.

If his conclusions be correct, the formation of heat in the brain must be very great, in order to raise the temperature of the whole organ and of the blood which is constantly coursing through its substance and carrying away the heat, above the general temperature of the arterial blood.

Hitherto the formation of heat in nerve has been undemonstrable, even by the most delicate means (Rolleston³). The

¹ BRITISH MEDICAL JOURNAL, July 27th, 1895, p. 211.

heat, therefore, which is produced by the brain as a whole must owe its origin, as Mosso suggests, to the activity of the nerve cells, and the small amount of cortex must be capable of generating sufficient heat to raise the temperature of the whole brain above that of the aortic blood which is continually circulating through it.

One objection to Mosso's methods of investigation is that it is difficult to ascertain the true temperature of the blood in the carotid artery, as has been shown by one of us (Hill) in a research with W. M. Bayliss.⁴ Mosso employed the thermometric method. Now Bayliss and Hill found that the temperature recorded by a delicate long-stem thermometer, such as Mosso used, depends not only on the temperature of the tissues in which the bulb is placed, but also upon the temperature of the tissues in which the stem lies, and upon the length of the stem uncovered by the tissues. If a thermometer be pushed down the carotid into the aorta, the bulb lies in the aortic stream and is at aortic temperature, but the stem lies in the carotid artery in which no blood is circulating, and which is not far removed from the cooling external surface of the body. The thermometer, therefore, does not record the true aortic temperature, but a somewhat lower one. If the bulb and stem of a thermometer sunk in the brain be more favourably placed and be more protected from cooling influences than the thermometer in the aorta, the brain may appear hotter than arterial blood, and then any increased determination of arterial blood to the brain would tend to make this apparent difference still greater.

The cerebral circulation changes passively with every alteration of the general arterial or venous blood pressure (Roy and Sherrington⁵ and Bayliss and Hill⁶). We have found that an epileptic fit produced by cortical excitation or by administration of absinthe has an enormous effect on the cerebral circulation and on the general distribution of blood in the body. Mosso employed these methods to obtain elevations of temperature in the brain during the activity of that organ, therefore many of the recorded changes of cerebral temperature may have been caused by the determination of arterial or venous blood to the brain through those changes in blood pressure which were produced by his experimental methods. It will be remembered that Claude Bernard⁷ and later Heidenhain⁸ found that the blood in the right side of the heart is considerably warmer than aortic blood. It seems to us that the precautions taken by Mosso to eliminate the source of error here indicated were not sufficient. On the other hand, the blood which flows from the venous sinuses when the torcular Herophili is opened is less venous in colour than that of the femoral vein. Mosso's conclusions seemed entirely opposed to this fact, and led us to investigate the relative exchange of blood gases in the brain and in muscles.

METHOD.

The research was carried out by means of the simple form of gas-pump devised by one of us (Hill⁹). Before beginning the actual determinations, the accuracy of the pump was re-investigated, and the working error found to be less than 1 per cent., which is quite compensated for by the simplicity of the pump and the rapidity of action. Another advantage of this over the older pumps of Ludwig and Pflüger is that 8 to 10 g. of blood are sufficient for each sample, and this quantity can be drawn simultaneously and rapidly from an artery and vein, the condition of the animal meanwhile remaining uniform. In the older methods of Ludwig and Pflüger, 50 to 60 c.cm. of blood were necessary for each determination. Both the abstraction of so large a quantity of blood and the long time necessary for its collection are factors against the animal's condition remaining uniform.

At the beginning of our research we collected first an arterial and then a venous sample of blood. In the state of rest, the condition of the animal remaining, as we found, remarkably constant, this method of procedure was quite legitimate. But later on, when we came to investigate the blood in the active condition provoked by the injection of oil of absinthe, we found that the gases of the carotid blood varied considerably during the alterations in respiration consequent upon the development of the fit. We therefore changed our method, and in states of rest and of activity (tonic and clonic spasms) collected the samples of carotid blood simultaneously with the venous samples. We thus

obtained in each case samples of blood going to and coming from the brain or muscles. The arterial blood was obtained from the carotid artery. Ludwig, Pflüger,¹⁰ and others have shown that the gases in carotid and femoral blood are practically the same. In order to obtain the cerebral venous blood, the torcular Herophili was trephined, and the blood from the superior longitudinal sinus allowed to flow directly into the small blood bulbs shortly to be described. We always obtained the blood direct from this sinus, for we invariably found that if a clot formed at the opening of the superior longitudinal sinus the bulb refused to fill. The venous blood from the muscles was obtained through the deep femoral vein.

The samples of blood (8 to 10 g.) were collected in small bulbs, rinsed through with oil. The blood was then immediately transferred to the vacuum froth bulbs of the pump, and defibrinated by shaking with mercury. The froth bulbs, after the necessary weighing, were kept in the cold until the gases were extracted. This method of procedure was necessary, as it was impossible to draw the blood straight from the torcula into the vacuum froth bulb. It was found, however, by experiment that the percentages of blood gases were unaltered by using these small blood bulbs. The animals employed were exclusively dogs, and the experiments carried out under morphine narcosis. First a pair of samples (arterial and venous) was collected during the state of rest, and then, after injection of absinthe, the pairs of samples were taken during the tonic and clonic stages of the fit.

RESULTS.

As a result of six consecutive experiments with carotid artery and torcula, we found that during rest the average difference of CO₂ in artery and torcular = 3.87 per cent. and of O 3.42 per cent. as against 4.06 per cent. CO₂ and 4.95 per cent. O in the tonic and 2.99 per cent. CO₂ and 4.31 per cent. O in the clonic stages respectively. Similarly as a result of 8 consecutive experiments with carotid artery and femoral vein, we found that during rest the average difference of CO₂ = 8.76 per cent. and of O 12.92 per cent. as against 13.90 per cent. CO₂ and 13.75 per cent. O in the tonic and 19.33 per cent. CO₂ and 12.63 per cent. O in the clonic stages respectively. These numbers may be tabulated thus:

		Rest.	Tonic.	Clonic.
CO ₂	Torcula ...	+ 3.87	+ 4.06	+ 2.99
	Femoral vein ...	+ 8.76	+ 13.90	+ 19.33
O	Torcula ...	- 3.42	- 4.95	- 4.31
	Femoral vein ...	- 12.92	- 13.75	- 12.63

It will be seen at a glance that the metabolism of the brain is very low, and that it is scarcely increased during the stages of an epileptic fit. The metabolism of the muscles, on the other hand, is two or three times as much as that of the brain during rest, and is greatly increased in both the tonic and clonic stages of the fit.

The result is manifest without taking into account the rate of blood flow. Chauveau and Kaufmann¹¹ estimated it to be three times as fast from active as from resting muscles. From our own observations on the time that the blood bulbs take in filling, we are led to believe that the rate of flow through the muscles is from twice to six times as fast during a fit as in the state of rest; and from the experiments of Stewart¹² we gather that the rate of flow of the blood through the brain is approximately the same as through the muscles of the leg. If we therefore multiply our results by some number between 2 and 6 the metabolism of active muscle will become enormously greater than that of the muscle in rest.

CONCLUSIONS.

From the above experiments it is clear that our results do not bear out the conclusions of Mosso, for it would appear that, when compared with the muscles, the brain is not a seat of active combustion, and considering the very small increase in CO₂ in the torcular blood, it seems to us very improbable that the temperature of the brain should be perceptibly greater than that of the blood.

Summary of all the Experiments in the State of Rest and Morphine Narcosis.

Average of 52 arterial samples	=CO ₂ 37.64 per cent.; O 18.25 per cent.
" 42 torcular samples	=CO ₂ 41.65 per cent.; O 13.49 per cent.
" 28 femoral vein samples	=CO ₂ 45.75 per cent. O 6.34 per cent.

Average Differences.

Carotid artery—torcular =CO₂ 4.01 per cent.; O 4.76 per cent.
 —femoral vein=CO₂ 8.11 per cent.; O 11.91 per cent.

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REPORT ON

THE EFFECTS OF REPEATED HÆMORRHAGES ON THE COMPOSITION OF THE BLOOD.

By ARTHUR H. WHITE, L.R.C.P. & S.I.

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THE quantity of blood withdrawn was in each instance carefully estimated, and analyses of the various constituents were made, and then twenty-four hours afterwards a further careful bleeding and series of analyses and so on. The number of the successive bleedings in the case of the individual dogs varied from two to four. The analyses comprised the amount of water and solids, total proteids, fibrin, ash and ether extract, while in addition estimations were made of the corpuscular elements, the quantity of hæmoglobin, the specific gravity, and the coagulability. Investigations were made of the nature and character of the blood corpuscles, and also in one or two instances the histological changes in the glands, marrow, spleen, liver, etc., were partially examined.

Naturally in a research of this kind necessitating the immediate and simultaneous estimations of so many different things, some of the methods employed were not of the most exact nature, though sufficiently exact to give an approximate idea of the alteration; mostly, however, the method of analysis was as precise as possible—this being especially true in the cases of the water and solids, specific gravity, total proteids, fibrin, and ether extract.

The various points which I reported last year in regard to the disturbance in the relationship of the water and solids, the reduction in the specific gravity and in the proteids, the progressive increase in the fibrin, etc., have been amply confirmed by my later results, and are now ready for publication.

Below is a table giving the full results in the case of one of the dogs.

In addition to these results certain facts which bear on the question of blood regeneration have been elicited, and with regard to the regeneration or replacement of the red corpuscles, it would appear that in certain cases when the serum becomes too poor in solids there seems to occur at first an actual dissolution of many of the red corpuscles which had been left. This certainly appeared to have resulted in one case twenty-four hours after an excessively large quantity of blood had been taken away, as the reduction in the number of the corpuscles was far greater than was warranted by the amount of blood lost.

With regard to the histological changes in the organs resulting from these acute hæmorrhages I can as yet report no definite results. I may, however, mention that in two of the cases, one of which was the animal referred to above, the amount of blood pigment in the spleen and liver was larger than normal. There is, of course, always a marked decrease in the number of corpuscles, but this only affects the red, as there is almost always a marked leucocytosis.

For the examination of the blood on each occasion of bleeding from a dozen to a dozen and a-half coverslip preparations were prepared according to Ehrlich's method, and subsequently were stained with all the various stains recommended by Ehrlich and his pupils for the exhibition of the various classes of granules, but were singularly productive of negative results. Despite the increase in the white corpuscles I found that so far as the eosinophile granules are concerned the cells containing them were certainly not more than proportionately increased; this is quite in accordance with Ehrlich's statement that in acute leucocytosis the eosinophile cells are, if anything, lessened. The neutrophile granules I never found either in the normal or altered blood; Ehrlich himself states they do not occur in dogs' blood.

The increase in the number of leucocytes seems to be chiefly, if not altogether, due to an increase of the so-called polynuclear leucocytes, for in these cases they form, instead of the normal 75 per cent. or thereabouts, in some instances as much as 95 per cent. of the whole. Nucleated red corpuscles I never found unless in cases where the animals had been bled three or four times, and then only exceedingly rarely.

With regard to the hæmatoblastic crisis said to occur after hæmorrhage, I can say that in many instances there would appear to be an increase of the blood plates, in some few cases a marked increase. Whether such elements, however, previously existed in the circulating blood, or only appeared in the blood after withdrawal, is a matter of doubt.

REPORT ON

THE ACTION OF DRUGS ON THE LEUCOCYTES OF THE BLOOD.

By GEORGE WILKINSON, M.D.

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I.—CHANGES IN THE NUMBER OF LEUCOCYTES.

DURING recent years several observers have recorded certain changes which take place in the number of the leucocytes of the blood of animals after the injection, either subcutaneously or directly into the circulation of bacteria, bacterial products, nuclei, peptone, and other substances. Acting on the suggestion of Professor Boyce, to whom I take this opportunity of expressing my thanks for much kind assistance, I have performed a series of experiments with a number of drugs, which were administered to rabbits by hypodermic injection, with the object of observing any changes that might occur, not only in the total number of leucocytes in the circulating blood, but also in the relative proportion of the mononuclear and polynuclear varieties.

	Blood Lost.		Weight of Dog in Kilos.	Specific Gravity.	In 100 parts of Blood.					Coagulation Time.	Hæmoglobin to Standard	Number of Red Corpuscles in 1 c.mm.	Proportion of White to Red.
	Grammes.	Percentage of Body Weight.			Solids.	Proteids.	Fibrin.	Ash.	Ether Extract.				
Normal blood	0.0	0.00	18.4	1052	17.85	15.04	0.37	0.81	0.13	—	94	5,730,000	1:690
Twenty-four hours after 1st bleeding ...	508.5	2.76	17.5	1048	17.06	14.53	0.41	0.81	—	45 to 50	66	4,490,000	1:457
„ „ „ 2nd „ ...	284.5	1.62	17.4	—	14.44	13.00	0.52	0.50	0.17	150 to 160	54	3,170,000	1:352
„ „ „ 3rd „ ...	252.0	1.44	17.2	1042	12.26	11.47	0.63	0.69	—	65	38	1,380,000	1:150
„ „ „ 4th „ ...	654.0	3.80	*	—	—	—	—	—	—	—	—	—	—

* On this occasion the animal was bled to death.