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OF THE
BRITISH MEDICAL ASSOCIATION.

Held at Carlisle, July 28th, 29th, 30th, and 31st.

PROCEEDINGS OF SECTIONS.

**SECTION OF PATHOLOGY AND
BACTERIOLOGY.**

Professor SHERIDAN DELÉPINE, M.B., President.

**A DISCUSSION ON THE PATHOLOGY OF
EXOPHTHALMIC GOITRE.**

I.—GEORGE R. MURRAY, M.A., M.D.Camb., M.R.C.P.,
Heath Professor of Comparative Pathology in the University of Durham;
Physician to the Royal Infirmary, Newcastle-on-Tyne.
THE pathology of exophthalmic goitre has attracted attention, and has been a subject for discussion since the disease was first described by Graves. The importance of the subject is evident, for future advances in our methods of treating the disease will largely depend upon a clear explanation of its pathology. It will, therefore, be useful to consider the subject in the light of recent experimental research and clinical observation in order to obtain a clear expression of opinion upon the main points which require further explanation.

When we examine a typical case of exophthalmic goitre we find that the most prominent symptoms are the goitre, the exophthalmos, the tachycardia, the various nervous symptoms, and the condition of the skin. As a natural consequence the heart, the nervous system, and the thyroid gland have each in turn been considered to be primarily at fault, and different theories based upon some observed or suspected morbid change in one or other of these organs have from time to time been advanced in order to explain the phenomena of the disease.

Few, if any, now maintain that exophthalmic goitre is primarily a disease of the heart, for it is generally allowed that the cardiac symptoms are secondary to disease of either the nervous system or thyroid gland. We thus are left to consider whether the disease is really due in the first instance to morbid changes in the nervous system or in the thyroid gland.

Many symptoms which occur clearly indicate that the normal functions of the nervous system are deranged, but this is not evidence of the existence of definite changes in the structure of any part of the nervous system, as all these symptoms may well be the result of the action of some toxic agent or of some altered state of nutrition upon the nerve centres. When we examine the records of cases in which the nervous system has been thoroughly examined, we are at once struck by the fact that in many cases no lesion has been found. On comparing the accounts of those cases in which a definite lesion has been found we find that the lesions described vary considerably in different cases, though each one may be definite enough in itself.

Some have regarded the sympathetic system as at fault, on account of the character of many of the nervous symptoms, and because a slight exophthalmos can be produced by stimulation of the sympathetic. There is, however, no anatomical basis for this theory, for the changes which have been described in the sympathetic are only those which may occur in health or in other diseases.

There is much more evidence to support the view that exophthalmic goitre is due to some primary lesion of the medulla. Thus Filehne¹ found that section of the anterior fourth of the grey matter of the restiform bodies was followed by exophthalmos. In some of his experiments both enlargement of the thyroid gland and exophthalmos occurred, and in one case tachycardia as well. Bienfait² made bilateral transverse sections through the grey matter of both restiform

bodies in rabbits. This was followed by marked alteration in the cardiac rhythm and a fine regular tremor. Exophthalmos was present in rather more than one-third of the animals used, and in one-fourth of them distinct hyperæmia of the thyroid gland appeared. These experiments show that some of the symptoms of exophthalmic goitre may occur as a result of interference with the normal action of the nerve centres in the medulla. In connection with these experiments an interesting case mentioned by Mannheim³ may be referred to in which exophthalmic goitre developed a few days after the onset of a bulbar haemorrhage and improved as absorption of the blood-clot took place.

The medulla has been carefully examined in a considerable number of cases of exophthalmic goitre and in some cases definite changes have been found. Thus subserous haemorrhages were found on the surface of the floor of the fourth ventricle by Bruhl and by Lasvènes. Numerous haemorrhages were found by Hale White in the medulla of one case; they have also been found by other observers. It is very doubtful if these small haemorrhages are of any pathological importance, as they are not infrequently found in cases in which no symptoms of exophthalmic goitre have occurred. Mendel found atrophy of the left restiform body and of the right "solitary bundle." On the other hand, Müller and others have found no signs of disease of this part of the nervous system in the cases examined by them, and Möbius states that as a rule no lesion of the medulla is found. It is thus evident that the changes which have been described are by no means constant, and so we cannot regard them as the cause of the disease.

The thyroid gland is more obviously diseased than any organ in the body of a person suffering from exophthalmic goitre, and I know of no case on record in which it has been found to be normal in structure when examined after death. We shall briefly consider the changes in structure which are found and compare them with other morbid changes, the results of which are well known. Let us compare the normal gland first with one which has been rendered almost functionless by extensive fibrosis, then with one which has undergone compensatory hypertrophy, and so is in a condition of unusual activity, and finally with a gland removed from a patient suffering from exophthalmic goitre.

The normal gland is composed of a number of closed follicles of various sizes lined by cubical epithelial cells and surrounded by connective tissue in which lie lymph spaces and blood vessels. The central part of each alveolus is filled by the colloid substance which is secreted by the epithelial cells. This secretion escapes into the lymphatic spaces, either in consequence of rupture of the wall of the alveolus or by minute channels which pass between the epithelial cells. From the lymph spaces it passes into the blood by the lymphatic vessels. The general appearance of the gland is shown in Fig. 1. Now compare this with the appearance presented by the thyroid gland of a patient suffering from myxedema, for which I am indebted to Dr. Calcott of Gosforth. Here we see an advanced stage of fibrosis of the gland. Only three alveoli are left in the portion represented in Fig. 2, and even in them the epithelial cells have to a considerable extent either undergone partial degeneration or disappeared altogether. All the rest of the field is occupied by dense fibrous tissue and masses of small round cells. It is obvious that this gland must have been nearly functionless.

As an illustration of the changes which take place in the thyroid gland when a part of it undergoes hypertrophy so as to respond to the demand for increased secretory activity caused by the removal of the rest of the gland, we may take the following experiment⁴:—On January 5th, 1894, the thyroid gland was removed from a Rhesus monkey while under the influence of ether. Subsequent events proved that a piece of the gland was accidentally left behind, so that instead of a complete thyroideectomy only a partial one was in reality performed. The wound healed by first intention, and the only changes noticed in the animal afterwards were slight hebetude, increased stupidity, and harshness of the voice. In March, 1895, fourteen months after the operation he developed general tuberculosis and was therefore killed. A piece of thyroid gland, weighing 0.42 grammes, was found on the right side, evidently a piece

¹ Erlanger Sitzungsberichte, 1879.

² Bulletin de l'Acad. Royale de Médecine de Belgique, 1890.

³ Der Morbus Gravesii, Berlin, 1894.

⁴ The expenses of this experiment were partly defrayed by a grant from the Scientific Grants Committee of the British Medical Association.

of the original gland which had hypertrophied. The pituitary gland weighed 0.05 grammes. Fig. 3 represents a portion of this piece of hypertrophied thyroid gland. The

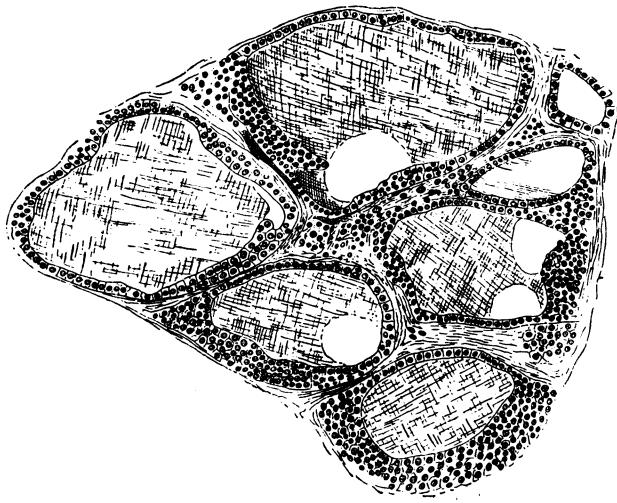


Fig. 1.—Normal thyroid gland. Drawn through Zeiss obj. D. Oc. 2, with camera lucida.

most important changes are : 1. The formation of new alveoli, some of which are filled by the epithelial cells. 2. Folding of the wall of the alveoli in some places so that the internal surface of the epithelium is increased in extent. 3. A change of the epithelial cells from a cubical into a columnar form. Compared with the normal thyroid gland of the monkey we have here clearly the appearances presented by a gland which is working at high pressure somewhat in the same manner that the mammary gland shows signs of unusual activity during lactation.

Fig. 4 shows the changes which were present in one lobe of the gland which was removed from one of my patients by Mr. F. Page of Newcastle. There is evidently a great increase in the amount of secretory tissue as compared with that in the normal gland (Fig. 1), for the number of alveoli is in-

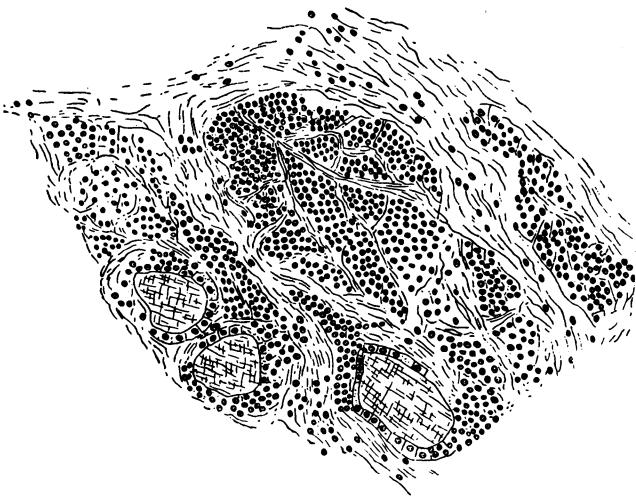


Fig. 2.—Fibrosis of thyroid gland from case of myxoedema. Zeiss obj. D., Oc. 2, camera lucida.

creased, and in some places the alveoli are filled with epithelial cells and show no central space filled with colloid, so that in any given area of the gland there are many more secreting cells than in health. The epithelial cells themselves are also changed, for instead of being cubical they are increased in size and columnar in type. There is less colloid substance to

be seen than in health ; this is probably due to increased rate of removal from the gland.

On comparing these different specimens it is evident that the thyroid gland in exophthalmic goitre differs greatly from the normal gland, and still more widely from the cirrhotic

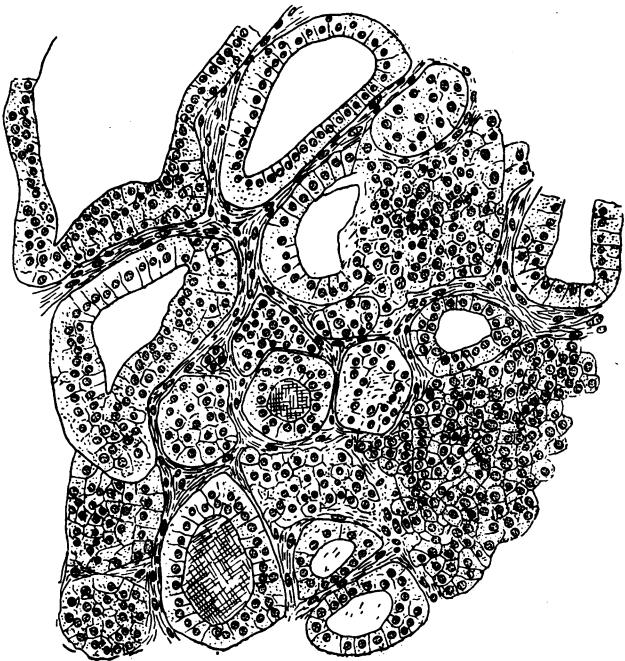


Fig. 3.—Compensatory hypertrophy of thyroid gland of monkey. Zeiss obj. D., Oc. 2, camera lucida.

gland in myxoedema. On the other hand it has a strong resemblance to the portion of gland which has undergone compensatory hypertrophy and which is in a condition of over-activity. The microscopical appearances thus indicate that bulk for bulk the thyroid gland in exophthalmic goitre

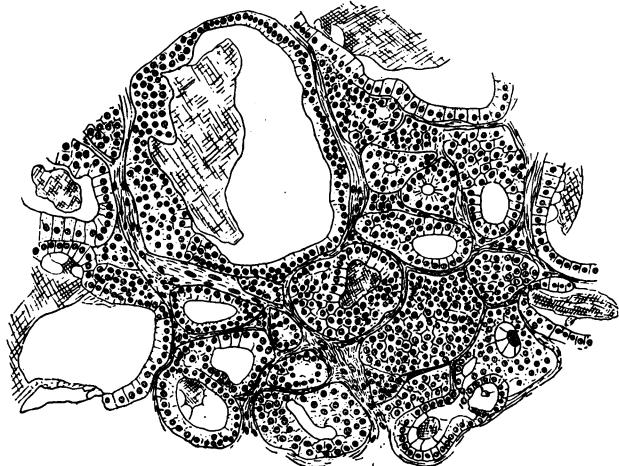


Fig. 4.—Thyroid gland exophthalmic goitre. Zeiss obj. D., Oc. 2, camera lucida.

is in a state of much greater activity than in health, and when we consider that in the great majority of cases the whole gland is considerably enlarged, it is evident that the total amount of secretion formed and absorbed may be many times greater than in health.

We know very little about the nature of the secretion of the thyroid gland in exophthalmic goitre. It is probable that it is altered in quality as well as in quantity, but this is a ques-

tion which must be left for future investigation to decide. All I wish to show is that we have a satisfactory anatomical basis for the view that the symptoms of the disease are due to an over-activity of the gland. Just as the structural changes in the thyroid gland in exophthalmic goitre differ as widely from the normal in one direction as those found in myxedema do in the other, so also we find that the symptoms of the two diseases offer a striking contrast, as has often been pointed out before by others as well as by myself.⁵ The symptoms, in fact, are such as we might expect to be caused by over-activity in the gland as compared with those which we know are due to deficiency or loss of function.

Still further physiological evidence in favour of this view is afforded by the effects which are produced by overdoses of thyroid extract in cases of myxedema and in healthy persons. Many illustrations of this have been given, so that it will be sufficient to take the remarkable case recorded by Béclère⁶ as an illustration. A woman aged 31, suffering from myxedema, took by mistake 92 grammes of thyroid gland in eleven days. The symptoms which developed were tachycardia, rapid respiration, exophthalmos, brilliancy of the eye, transient tremor of the arms, rise of temperature, insomnia, polyuria, glycosuria, albuminuria, and partial paraplegia. Many similar cases have been observed, showing that the symptoms of thyroid intoxication or thyroïdism are similar to those of exophthalmic goitre. Another important fact is the improvement which follows operations which are undertaken in order to diminish the secretory activity of the enlarged gland either by actual removal of a part of it or by ligation of some of the arteries which supply it. Great improvement has followed in some cases and recovery in others. I have recently seen a case which has been cured by iodine injections, a fibrosis having been set up by the iodine, which has cured the disease.

Still further evidence is afforded by those cases of exophthalmic goitre, a considerable number of which have now been recorded, in which, owing to the development of fibrosis, gradually leading to loss of the function of the gland, the symptoms of exophthalmic goitre have been replaced by those of myxedema. In such cases the symptoms of exophthalmic goitre first disappear, and it is only at a later stage that myxedema is developed. It appears then that the progressing fibrosis is at first really curative in nature, as it lessens the activity of the thyroid gland, and the exophthalmic goitre disappears. If the fibrosis progresses too far the functions of the gland become too much impaired, and more or less myxedema is developed, according to the amount of injury done to the secreting tissue by the fibrosis.

In conclusion I would maintain that in exophthalmic goitre there is an excessive formation and absorption of thyroid secretion, which may or may not be normal in character, and that the symptoms of the disease are due to the presence of this excess of secretion in the blood, and to its action upon the tissues and especially upon the nerve centres in the medulla.

The practical conclusion from this is that we should endeavour to improve our methods of treating the diseased thyroid gland. We want to be able to induce a moderate degree of fibrosis, and so imitate the natural process of recovery. Removal of a portion of the gland, though most successful in some cases, has proved to be a dangerous operation in others. Possibly injections of iodine, electrolysis, or some similar means of starting a limited fibrosis, may help us to attain the object we have in view without danger.

II.—VICTOR HORSLEY, F.R.C.S., F.R.S.,

Surgeon University College Hospital and to the National Hospital for the Paralysed and Epileptic.

MR. VICTOR HORSLEY wished to confirm the description given by Dr. Geo. Murray, Mr. Edmunds and Dr. Abram. He showed microphotographs of preparations made by him in 1886 of sections of thyroid glands in a state of compensatory hypertrophy showing the overgrowth of the secretory epithelium and the increasingly racemose character of the acini themselves. His anatomical observations thus were in exact accord with the more complete investigations of the investi-

⁵ *Twentieth Century Practice of Medicine*, vol. iv.

⁶ *La Semaine Médicale*, 1894, p. 462.

gators mentioned and the functional disturbance appeared to be a perversion of the secretion of the thyroid.

III.—WALTER EDMUND, M.C., F.R.C.S.,

Resident Medical Officer St. Thomas's Home, St. Thomas's Hospital.

THE first point to be considered in discussing the pathology of Graves's disease is the nature of the changes in the enlarged thyroid gland. These changes consist in (1) Enlargement of the individual vesicles. (2) The enlarged vesicles are oblong and branched, not globular. (3) The lining membrane is convoluted. (4) The secreting cells lining the vesicle have become columnar instead of cubical. (5) The secretion is less colloid and more mucilaginous: it does not stain so deeply with the usual reagents. Now these changes are practically identical with those found in a hypertrophied portion of thyroid in an animal produced by the excision of a portion of the thyroid; the remaining part hypertrophies; these changes in animals then are due to compensating hypertrophy. In Graves's disease, too, the changes in the thyroid are due to compensating hypertrophy; in other words, the change in the thyroid is not the primary lesion. This, too, tells against the view that the pathology of the disease is due to an excessive secretion of normal thyroid juice because if there were there would be no occasion for a compensating hypertrophy. It is certainly very natural to conjecture that, as myxedema is due to a decrease of thyroid secretions, Graves's disease is due to an excess; but there are objections to this theory. First, although the contrast between the symptoms of Graves's disease and myxedema is well marked in the chronic forms, in the acute form (as seen in dogs) it is not at all marked; indeed the two affections resemble one another. In both these are well-marked tremors and occasional attacks of dyspnoea. Secondly, the theory of excessive secretion will not explain the exophthalmos: the injection subcutaneously of thyroid extract in large quantities into monkeys does not produce exophthalmos in these animals, although the condition can be readily enough produced in them by the injection of cocaine. Thirdly, the theory will not explain how in many recorded cases the exophthalmos is on one side, or mainly on one side and the enlargement of the thyroid more marked on that side. Fourthly, the not uncommon occurrence of myxedema following Graves's disease seems to support the secretion view: but the theory would require an interval of good health in the transitional stage. One finds mention of cases in which the two diseases appear to co-exist. I recently saw a case in which this condition possibly existed and which improved while taking thyroid extract. Finally, against the secretion theory is the effect of thyroid feeding: different results have been obtained and the majority of observations seem to show that the treatment does no good, but it does not seem to do harm with the certainty that might be expected were the symptoms due to an excess of thyroid secretion. The secretion of the enlarged thyroid of Graves's disease is probably abnormal, but its physiological effect has not, as far as I know, been recorded; it would certainly be desirable when the opportunity presents to determine this point by experiment. Besides the thyroid being enlarged, the thymus is also enlarged: if this condition occurs in a considerable number of cases it has some important bearing on the pathology. Microscopically the enlarged thymus contains—(1) a large number of lymphocytes; (2) the concentric corpuscles of Hassell seem to be enlarged and in an active condition somewhat inconsistent with the view that they are fetal remains with no part to play in the organism; (3) here and there numerous eosinophile corpuscles are found. The pathology of the disease must be partly nervous and partly humoral: the exophthalmos must be produced in some way through the nervous system, and on the other hand it is difficult to see how a removal of a portion of the enlarged thyroid gland can act directly on the nervous system. It is possible that the primary lesion is a derangement of the metabolism of the body.

IV.—D. J. HAMILTON, M.D.,

Professor of Pathology in the University of Aberdeen.

PROFESSOR HAMILTON said that the condition of the thyroid gland described by Dr. Murray and Messrs. Horsley and Berry was of great interest, as showing the great

power the gland had of reproducing itself and as bearing on goitrous affections generally. The process seemed to be closely allied to that of adenoma in other glandular structures. The speaker had had an opportunity of examining the reproduced gland in man where partial excision had been practised in a case of ordinary goitre. The state of the reproduced gland was identical with that of the original tumour and closely corresponded with that described in the previous communications. A remarkable point noticeable in the reproduced gland was the small quantity of colloid contained in the vesicles. It would be of great interest if any of those taking part in the debate would give the results of their analysis of the colloid found in the thyroid as compared with the so-called colloid found in cancerous tumours and ovarian cysts. The nature of these colloid substances was still worthy of further investigation notwithstanding what had been done lately in the determination of their composition, more especially abroad. The sympathetic enlargement of the thymus in certain instances of exophthalmic goitre was a very curious phenomenon. The numerous cases of this coincidence put on record placed it beyond doubt that the tumour found lying over the pericardium was truly an enlarged thymus and not merely an hypertrophied supernumerary thyroid. In one case examined by the speaker the structure of the tumour seemed to be very much that of the ordinary thymus.

V.—J. G. ADAMI, M.D.,

Professor of Pathology, McGill University, Montreal.

PROFESSOR ADAMI said that while appreciating the President's invitation to take part in the discussion he felt that what during the last few years had rendered the Pathological the most satisfactory and most fertile Section of the Association had been that only those who had made researches upon the subject under debate have taken part in these discussions, and thus the work of the Section had not degenerated into the commonplaces of the ordinary meetings of learned societies or into mutual admiration. Not having made investigations directly upon the subject-matter of this discussion, he would not occupy the time of the section by a mere statement of opinions. He agreed on the whole with the views enumerated by Dr. Murray. With Professor Hamilton he held that more investigations were needed upon the nature and modifications of colloid in Graves's and other diseases and changes in the thyroid. That colloid was truly a secretion he felt more and more convinced. He had regularly examined the thyroids of the cases coming to the *post-mortem* theatre at the Royal Victoria Hospital during the last eighteen months, and had been greatly struck in the first place by the frequent tendency towards localised hypertrophy of the gland, in the second by the great variation in the condition of the contents of the vesicles. In man, as in the dog, the clear vesicles or droplets of secretion lying immediately upon the surface of cubical cells were frequently to be observed—an appearance only to be accounted for by the supposition that the thyroid epithelium has important secretory functions. Very frequently, apart from clinical symptoms of tachycardia or Graves's disease, he had noted the absence of proper colloid in the vesicles of the gland. While therefore he was inclined to believe that study of the nature and modifications of the thyroid secretions must lead to the most full knowledge of the intimate nature of Graves's disease, he would urge caution in ascribing only to the latter disease histological changes which fuller study of thyroid glands in general would show to be common to other conditions.

VI.—J. HILL ABRAM, M.D.,

Assistant Physician to the Liverpool Royal Infirmary.

My own work has been done with material from the *post-mortem* room and operating theatre. The nervous system in the two fatal cases was normal, the thyroid glands showed the changes described by Dr. Murray. In a case operated on by my colleague, Mr. Paul, the colloid matter was abundant, the blood vessels, so to speak, being bathed in a sea of colloid. The active principle is a pure secretion in all probability as shown by the absence of mitoses in the active gland. The thyroid theory is further supported by the results of operations tending to the diminution of the secretory area.

VII.—ROBERT HUTCHISON, M.D., M.R.C.P.Ed.,
Chemical Assistant to the Professor of Physiology, University of Edinburgh.

DR. HUTCHISON remarked that up till now the chemical aspects of the pathology of exophthalmic goitre had been almost entirely neglected. This was no doubt due to our ignorance of the chemistry of the thyroid. Recently, however, great advances had been made in our knowledge of the chemistry of the normal thyroid and of its active ingredient which necessitated a reconsideration of current views on the pathology of exophthalmic goitre. Dr. Hutchison then considered briefly the chief points in the chemistry of the thyroid, and insisted upon the fact that his own observations, both experimental and clinical, led to the conclusion that the colloid matter of the thyroid is its only active ingredient, Baumann's thyroïdin being a product derived artificially from the colloid and representing only a part of the activity of the latter. He had entirely failed to confirm Fraenkel's views regarding the presence in the thyroid of an alkaloidal substance. Granted that the colloid matter is the only active substance in the thyroid, those who hold that exophthalmic goitre is primarily a disease of that gland, must be prepared to show either (1) that there is an over-production of the normal secretion of the thyroid, that is, of the colloid matter; or (2) that there is a qualitative alteration in that secretion. As regards the first of these propositions, the fact was insisted upon that morbid anatomists are almost unanimously agreed that there is no increase of the colloid matter to be observed in the thyroid from cases of exophthalmic goitre, and there is no reason to believe that the secretion is more rapidly removed from the sacs in that disease than in the normal condition. The second proposition cannot, at present, be either proved or disproved by chemical means. The only feasible method is to try the physiological effects of the different ingredients of the gland from cases of exophthalmic goitre. This Dr. Hutchison stated he had done. He had obtained a large thyroid (weight 85 grammes) removed by operation from a typical case of exophthalmic goitre. By suitable treatment the different ingredients of the gland were isolated. These were administered to two female patients, both under 25 years of age, who were undergoing thyroid treatment, one for a skin affection, the other for obesity. The protein-free extract of the gland (containing the "extractives" and any alkaloidal substances that might be present) was found to be entirely inactive, even in doses equivalent to 14 grammes of the fresh gland daily. The colloid matter was then given. In doses equal to from $3\frac{1}{2}$ to $4\frac{1}{2}$ grammes (50–65 gr.) daily, it produced loss of body weight with slight rise of temperature and some acceleration of pulse. These symptoms were not more marked than had been produced by equivalent doses of sheep's thyroid in the same individuals. No palpitation was complained of in either case, nor was there the least degree of exophthalmos produced, or any appreciable alteration in the thyroid. To a dog from which the thyroid had previously been removed larger doses of the colloid (8 grammes of fresh gland daily, or about as much as $1\frac{1}{2}$ thyroid of an average sheep). The temperature and pulse showed a slight rise, but no other symptom was produced. As far as these observations went they were directly opposed to the view that the thyroid in exophthalmic goitre produced a peculiar secretion.

Dr. Hutchison then passed to a consideration of the arguments in favour of the thyroid theory of exophthalmic goitre, based (1) upon the contrast between the symptoms of myxoedema and those of exophthalmic goitre, and (2) upon the alleged fact that cases of exophthalmic goitre are aggravated by thyroid feeding. From the chemical point of view both these arguments were entirely fallacious. Any disease characterised by an exaggerated rate of metabolism would present a similar contrast to a disease such as myxoedema, in which general metabolism was abnormally slow. It would be found on consideration that the general symptoms of fever were just the opposite of most of the symptoms of myxoedema. It had been proved by experiment that thyroid feeding caused an increased metabolism in the tissues, and it was not to be wondered at if it should exaggerate the symptoms of such a disease as exophthalmic goitre in which metabolism was already too rapid. No one would expect fever to be benefited by thyroid feeding.

In conclusion, Dr. Hutchison was inclined to regard the disease exophthalmic goitre as consisting essentially in a specific change in tissue metabolism, probably due to a functional alteration in the central nervous system, the relationship of the enlargement of the thyroid to these changes being as yet undetermined, but not to be regarded as their primary cause. The beneficial effects of surgical operation in exophthalmic goitre were not necessarily opposed to this view. One might tumble downstairs both from the action of gravity and also because he was propelled by a kick from behind. Withdraw the propulsion of the kick and gravity itself would not start the descent. So it might be in exophthalmic goitre. Remove that tendency to acceleration of tissue metabolism which the normal secretion of the thyroid had been proved to produce, and even a functional loss of control on the part of the nervous system might be unable to start that train of metabolic changes which lead to the symptoms of exophthalmic goitre.

VIII.—BERTRAM ABRAHAMS, M.B., M.R.C.P.

DR. ABRAHAMS questioned Dr. Murray's statement as to the omnipresence of thyroid changes in exophthalmic goitre, pointing out that Gerhardt had in a recent paper¹ referred to cases in which no change was seen in the thyroid, but the spleen and other blood-forming glands were enlarged. Gerhardt considered the vascular changes (themselves probably caused by nervous disturbances dependent on altered metabolism) antecedent to those in the glands, and Dr. Abrahams could partially confirm this by reference to a case of his own, which improved markedly when treated with suprarenal extract, which is known to have a vaso-constrictor action. With regard to the influence of the thymus, he called attention to the good effects obtained of late in Germany by feeding with that gland. He also quoted Martius's² assertion that the colloid found in the thyroid in exophthalmic goitre was usually diminished in amount, and always chemically abnormal. The whole condition resembled that of a toxæmia, such as that seen in lead poisoning or uræmia, and this was in harmony with the sudden onset from apparently slight causes, such as fright.

DR. MURRAY'S REPLY.

DR. MURRAY thanked the speakers for their discussion and the meeting for its appreciation of his paper. The study of the evidence had not yet convinced him that myxœdema and exophthalmic goitre could coexist. He asked if Professor Gerhardt's remarks on normal thyroids in the latter disease did not refer to the clinical rather than the microscopical aspect. He considered that on collating all the cases the balance was in favour of thyroid extract being a harmful element in the treatment of Graves's disease. In reply to Dr. Ransom, Dr. Murray said that sudden death very often resulted (as in a case of his own) from the anaesthetic.

OBSERVATIONS ON THE SECRETION OF BILE.

By W. B. RANSOM, M.A., M.D., M.R.C.P.,
Physician to the General Hospital, Nottingham.

THE paper is based on the study (I) of a case of biliary fistula, in which all the bile escaped into a bottle, and (II) of the pigments of the urine and faeces in health and in various cases of disease.

The following are the main conclusions arrived at:

(I.) 1. The absence of bile from the bowels is compatible with a large appetite for all kinds of food—proteid, carbohydrate, and even fatty—and a steady increase in weight, from 9 st. to 9 st. 10 lbs. in six weeks.

2. The absence of bile does not cause constipation. The patient had daily two large, soft, white stools, loaded with minute fat globules, but no excess of meat or starch. Probably the undigested fat has a laxative effect. The stools were not especially offensive.

3. The average daily quantity of bile was, in May 35 ozs., in June 30 ozs. The secretion during the night and day was approximately equal, sometimes the former sometimes the latter being greater by 1 or 2 ozs.

4. The bile was invariably yellow when first passed. Reaction always alkaline. Specific gravity, 1008 to 1010; the night's bile was never lower, and usually higher, than that passed by day. The daily solids averaged about half an ounce.

5. No drugs were found to act as cholagogues. Rhubarb, calomel, salicylate of soda (3j daily), ox bile (gr. 70 daily), all failed to influence the quantity or the specific gravity of the bile. A very slight increase (2 ozs.) occurred after the administration of haemoglobin pills (100 gr. daily for a week).

6. The quantity of bile secreted appeared to vary inversely as that of the urine. It was slightly less on a diet of milk and farinacea than on a full meat diet.

7. The urine, after the bile pigment had disappeared from it, was of a pale yellow colour. No urobilin could be detected in it, but the pigment precipitated by ammonic sulphate when dissolved in acid alcohol was of a purple colour, and showed with the spectroscope a distinct band between D and E (λ 552 to λ 570) and a faint shading between F and b (λ 495 to λ 506), thus to some extent resembling the two-banded spectrum sometimes met with in haematorporphyrinuria; the neutral solution showed no band. After precipitation of urates by ammonium chloride no pigment showing bands could be found in the urine. No haematorporphyrin was obtained by Garrod's soda method or by Salkowski's barium chloride method. No change in colour or spectrum was produced in the urine by a daily dose of 100 gr. of haemoglobin.

8. From the white faeces rectified spirit extracted a yellowish pigment, not showing bands, possibly derived from the food. After the administration of haemoglobin by the mouth the stools became buff-coloured, and contained a small quantity of "urobilin" with some haematin.

(II.) 1. "Pathological" urobilin is "normal" urobilin present in increased amount. Some of its supposed properties are (as Hopkins has shown) due to admixture with haematorporphyrin. Urobilin in the urine is probably always derived from the bile, being absent when all the bile escapes from the body. It was found especially abundant in cases of hepatic congestion or cirrhosis, in some cases of jaundice without white stools, in some cases of typhoid fever, even after subsidence of the temperature to normal, and in a case of Graves's disease with severe diarrhoea but no fever. It was not found increased in pernicious anaemia, nor in a case of haemophilia with extravasations.

2. The pigment of the faeces (apart from that of food) consists of various and varying reduction products of bile, some of which give no bands in the spectrum. One, stercobilin, is identical with a concentrated solution of urobilin and is usually present. In one case of pernicious anaemia, hydrobilarubin, with two bands (λ 480 to λ 510, and λ 590, to λ 610) was found in its stead.

3. Urobilin in urine is probably mainly derived from stercobilin absorbed from the intestines. The fact that it was found in ascitic fluid in cases of portal obstruction but was not found in the fluid of pleural effusions supports this view.

In cases of hepatic disorder and of slight jaundice without white stools, it is possible that the urobilin of the urine may have its source in bile which has not reached the intestine, but has been reduced in the liver.

Dr. VAUGHAN HARLEY stated that he found in dogs, and so far as imperfect observation went, in man also, that there was not only decreased absorption of fat from the intestines, but also a diminution in the quantity of nitrogen absorbed. He agreed with Dr. Ransom that there were as many if not more cases of pernicious anaemia with pale urine, but thought even in these the urobilin was increased.

In reply to Dr. Harley, Dr. RANSOM said that he also felt strongly inclined to the view that all urinary urobilin was due to the absorption of stercobilin from the faeces, but there were some cases of hepatic and general disorder in which urobilin was increased without clear evidence of increased intestinal putrefaction, to which this view would not apply.

PRESENTATION.—A valuable clock and pair of vases has recently been presented to Mr. Arthur F. Gevis on his retirement from the post of Medical Officer to the Haverstock Hill and Malden Road Provident Dispensary.

¹ Mitteil. aus d. Grenzej. der Med. u. Chirurgie, I, 2.

² Berliner Klinik, May, 1896.

FORMATION OF UROBILIN.

By VAUGHAN HARLEY, M.D.,

Professor of Pathological Chemistry in University College, London.

SINCE Jaffe¹ first demonstrated the appearance of urobilin in the urine of patients suffering from febrile diseases, its pathological significance has attracted the attention of numerous workers.

Urobilin icterus was described by Gerhardt² in 1878; in which the skin instead of having the greenish-yellow colour of ordinary jaundice has a dirty yellow colour, and the urine gives no reaction with Gmelin's test but shows a marked increase of urobilin. Although in normal urine the quantity of urobilin is extremely small, there is always present in it either some of it or its chromogen. The chromogen, which is called urobilinogen, is converted on standing by oxidation into urobilin. A urine which at first yields no distinct band of absorption in the spectrum may, after the addition of an acid, show the urobilin band at F from the chromogen having been oxidised into urobilin. The normal quantity of urobilin as estimated by G. Hoppe-Seyler³ is from 0.8 to 0.15 grammes per kilo-weight in the twenty-four hours' urine. The late researches of Fr. Müller⁴ show that from mere traces it may rise to as much as 0.20 grammes. The quantity is greatly increased in the urine in cases of liver disease and where there is absorption of large blood extravasations, as well as in diseases where there is great breaking down of the blood corpuscles, such as occurs in fever, scurvy, and pernicious anaemia.

As it was thought that urobilin was either derived from the blood or the bile pigments, various conjectures were made to account for its increase in quantity in the urine in certain diseases. Since it is thought that in certain pathological conditions a diagnosis may be founded on the increase in the quantity of urobilin in the urine, a solution to the question of in what part of the organism it is formed is of very great importance, and the following is a brief summary of the theories that have been propounded up to the present.

1. *Hepatogenous Urobilin*.—The French are the chief supporters of this theory. They consider that instead of under normal conditions the liver cells forming bilirubin they form urobilin when they are diseased. The presence of an increase of urobilin in the urine they therefore consider arises from hepatic insufficiency.

2. *Hæmatogenous Urobilin*.—The supporters of this view consider the liver has nothing to do with the formation of urobilin, and that it is directly derived from the red blood corpuscles which are broken up in the circulating blood, either by some chemical or toxic poison. Or it may be that the breaking up of the red corpuscles in large extravasations yield urobilin to the circulation, which, like any other foreign substance, is eliminated from the blood by the kidneys.

3. *Nephrotic Urobilin*.—Those who believe that the kidney is the source of urobilin consider that bile from any cause, after reaching the general circulation, is converted into urobilin during the process of its elimination by the renal epithelium, and then finds its way into the urine. According to the quantity of bile that is to be eliminated, all or only part of it is converted into urobilin, and this explains why urobilin may be increased when bile pigments are absent, or nearly so.

4. *Histogenic Urobilin*.—In the same way as in the last view the bile in the organism itself is believed to be the precursor of the urobilin. The bile pigment, after having reached the general circulation, and being deposited in the tissues as in ordinary jaundice, is slowly converted into urobilin, and the urobilin being more soluble than the bile, is then dissolved in the blood and is eliminated in the urine.

5. *Enterogenous Urobilin*.—Maly, who long ago showed that urobilin could be formed from bilirubin by reduction outside the body, considered that in the healthy organism the urobilin in the urine is derived from absorption into the blood from the intestinal tract, of the urobilin that has been formed from the bilirubin in its passage along the intestines. The

late investigations of Müller and his pupil, D. Gerhardt, have added strong support to this last view. Müller found a method of separating bilirubin from urobilin either in the urine or the faeces, and by means of the spectrophotometer he was able to estimate the amount of urobilin. He found that in obstruction of the ductus choledochus, from either calculi, morbid growths, etc., where no bile entered the intestines, urobilin entirely disappeared from both the faeces and the urine, while immediately after the obstruction to the duct was removed, and the intestines again contained bilirubin, urobilin reappeared in the faeces and urine. From this he considered that urobilin is formed from the bile pigments in the intestine, from thence absorbed into the circulation, and then excreted with the urine. The following experiment seems to prove this point:

A man with marked jaundice, whose faeces contained no traces of urobilin, was given daily by a stomach tube from 25 to 125 g. of pig's bile absolutely free from urobilin. On the second day after its administration urobilin appeared in the faeces, and on the third day it was detected in the urine. The administration of the bile being stopped, the urobilin disappeared from the faeces and urine.

Müller considered that the increase of urobilin during the absorption of large blood extravasations and in infectious diseases where blood destruction is going on is due to the blood pigment while passing through the liver being converted into bile pigment, and thus causing an excess of bile pigment, which in its turn gives rise to an increased formation of urobilin in the intestines and absorption of it from them. The result of Müller's experiment supports Maly's view that the urobilin met with in the urine is derived from the urobilin formed in the intestines by the reduction of bile pigment.

I will now adduce some experiments of my own on the formation of urobilin in the intestines, and show that the increase of urobilin in the intestines must be accompanied by an increase of intestinal bacteria to produce any marked increase of urobilin, and by increased intestinal putrefaction, without increase of bile, urobilin may be increased in the urine. Whether or not under certain pathological conditions it can also be formed in the tissues or blood I am not at present prepared to discuss.

Schmidt⁵ showed that when a concentrated solution of perchloride of mercury is applied either to wet or dry faeces containing urobilin, in the space of a few minutes a bright rose-red colour is developed. The rose-coloured extract when separated and examined with the spectroscope shows the urobilin band between F and b.

In the presence of bile, in consequence of the conversion of bilirubin into biliverdin, the perchloride of mercury gives a bright green colour, so that this test is applicable to both substances. It is possible by this method to recognise very small quantities of urobilin. The colour is distinctly visible on a fragment of faeces after the treatment with perchloride of mercury when examined under the microscope, and until we had this method it was extremely difficult to recognise urobilin in small quantities in the faeces. On examining the different parts of the intestines and intestinal walls Schmidt found that the urobilin reaction yielded results differing not only in different parts of the intestine, but also in different cases.

In the small intestine he examined twenty-five cases in all, and found in one-third of them a faint red coloration in the upper part of the jejunum, both in the contents and in the wall. Most of the cases were children.

In another third of the cases examined the small intestine showed no red colouration whatever, or at the most only a faint pink colour towards the lower end of the ileum. In them the ileo-caecal valve was strongly demarcated by the deep colour of the caecum and the faint colour of the ileum. In the other third of the cases the colour stood between the two first mentioned.

With regard to the large intestine, the upper part, close under the caecum and in a few cases also the vermiform appendix, gave a deep pink coloration with the perchloride of mercury. This was less and less pronounced in the ascending transverse and descending colon. The red coloration of the walls slowly faded away until it entirely disappeared towards

¹ Centralbl. f. med. Wissenschaft., 1868.² Ueber Urobilinikterus. Korresp. des Allg. artzl. Vereins in Thüringen, 1878.³ Virchow's Arch., v. 124, 1891, p. 34.⁴ Ueber Icterus. Maly's Jahrs. d. Thierchemie, v. 22, 1892, p. 655.⁵ Schmidt, Verhandlungen d. Congress. f. innere Medicin, 1895, p. 320.

the sigmoid flexure. The contents of the large intestine, on the other hand, yielded a distinct pink colour as far as the anus.

The results I have obtained in the human subject are very similar. The contents of the various parts of the intestines were placed in small porcelain capsules and treated with the perchloride of mercury. The intestines themselves were likewise treated with the reagent after being well washed. The results obtained in this way led me to suppose that the urobilin reaction of the small intestines is not so well marked in the case of adults as Schmidt would lead one to suppose from what he obtained in the case of children. I found it to be very exceptional to find any urobilin coloration in the contents above the ileo-caecal valve.

Another interesting fact I noted which Schmidt drew no attention to is that the green or yellow colour due to the staining of the contents by bile in the duodenum and upper third of the jejunum tends to disappear about the middle third of the small intestine, where the contents become of a more or less greyish white; the green colour reappearing in the lower third of the small intestine as the contents of the ileum are always more or less coloured green with a slight tinge of brown. It would appear as if the bile in its passage along the intestinal canal is converted in the middle third of the small intestine into some colourless chromogen, to be reconverted into coloured bile lower down. For one can hardly suppose that all the bile pigment is absorbed from the upper part of the intestines in order to be re-excreted from the blood into the lower third of the small intestine.⁶

The urobilin coloration is only obtained when one reaches below the point in which the bilirubin has reappeared. A great part of the urobilin present in the intestinal contents is probably in the form of the chromogen urobilinogen, for from the results of analysis I find that larger quantities of urobilin are always to be obtained in the intestinal contents after they have stood a little while. This does not, however, entirely support the chromogen view of the case, as during the standing process after removal from the body the bacteria have a longer time to convert more bile pigment into urobilin.

In the case of a 12 days old child I had the opportunity of examining, through the kindness of Mr. Curtis, there was neither in the contents nor in the walls any urobilin obtainable. This result agrees with that of Schmidt, who could get no reaction in the case of a 5 days old child.

Müller found no urobilin in the urine of newborn children, and none appeared in either the faeces or the urine until three days after birth. In the case of the 12 days old child above mentioned, the descending colon, sigmoid flexure, and rectum contained only a little colourless mucus, and the caecum some greyish mucus but no urobilin. The upper part of the small intestine was bile-stained, and the middle third—as in the case of the adults—was almost colourless. The bile colour, however, reappeared in the ileum.

The staining of the wall of the caecum with urobilin is supposed to be partly due to *post-mortem* diffusion, and partly to an absorption of urobilin taking place around it.

The results I obtained in the other animals in which examination was made immediately after death led me to a contrary conclusion, and I consider the staining of the intestinal wall was not due to absorption, or any indication of absorption, but merely a *post-mortem* diffusion, for in none of the animals—such as cats, dogs, and monkeys—did I obtain any staining of the walls of the intestinal tract, as I did in those of the human body I examined some hours after death. When the *post-mortem* examination is delayed, one always obtains more or less marked staining in the case of the animals, as in man. Schmidt says he found the same staining occurs in pigs as in man, but does not state how long after death they were examined. The animals I experimented on were always treated in exactly the same manner, and were killed with chloroform, the ligatures being always placed round the different parts of the intestines before the bowels were removed from the body. The contents of each part were separately placed in small capsules, the perchloride of mercury solution added, and the appearance they presented at various times noted. The intestines themselves were always well washed to remove any adherent contents before being treated.

⁶ This colour change is not present in all cases and is, as a rule, most marked in dogs.

In the case of the dogs I found, as in man, the middle of the small intestine, as a rule, colourless. I will here give the results obtained in one case as a type of what was found in the others:

The contents of the duodenum immediately below the pylorus were colourless, but the bile staining extended somewhat above the entrance of the bile duct into the duodenum, and downwards from it the yellow colour of the contents in the upper third of the intestines slowly faded away till the contents of the middle third of the small intestine were merely of a greyish-white hue. The contents of the lower third of the small intestine again became slightly greenish, and retained more or less of a greenish colour, somewhat tinged with brown, until just above the caecum, at which point there was a suspicion of a fecal odour and tint. Immediately below the ileo-caecal valve the green colour of the contents disappeared, and both in look and smell they resembled dog's ordinary faeces. After standing the perchloride of mercury yielded the bright green of biliverdin in the upper and lower thirds of the small intestine, where the yellow colour of bilirubin was originally found, but no green coloration was obtained in the middle third. Just below the ileo-caecal valve the contents of the intestine gave with perchloride of mercury a marked urobilin reaction, and this continued to be the case as far down as the rectum. No colour reaction could be obtained in any part of the wall of the small intestine.

The dog now referred to had been fed on biscuit alone, with a little meat some twelve hours previously.

In the case in which the dogs were fed solely on meat, the colour met with in the middle third of the small intestines was more grey than white, and haematin could be chemically recognised in it. The same remark likewise holds good for cats.

In neither the normal dog nor cat have I been able to obtain in the intestinal contents much above the caecum any urobilin, and when examined while in a fresh condition the walls of the small intestines throughout showed no staining with urobilin whatever.

In a monkey I examined I found the same changes occur as I found in man. The urobilin was found present in the intestinal contents from below the caecum to the anus, but there was no trace of a pink coloration in the walls of the caecum, colon, or rectum.

The results obtained in the foregoing experiments led me to investigate the formation of urobilin in two dogs from which the large intestine and caecum had been removed four months previously. The small intestine having been artificially joined to the rectum, at the *post-mortem* examination the junction was found to be in one of the dogs (A.) 4 centimetres, and in another (B.) 6 centimetres above the anus. Both of these dogs, in spite of their having neither large intestine nor caecum during the latter months, partook heartily of a mixed diet of meat and biscuits, and appeared in the best of health. The bile and urobilin in the faeces was examined by the method of Gerhardt.⁷ The sulphates were estimated by Baumann's and the nitrogen by Kjeldahl's method.

In dog A., where the large intestine had been removed, the faeces appeared to the naked eye to contain large quantities of bile, and bile was always chemically found to be present in large quantities, and though urobilin was fairly present on some days, as a rule it was only found in small quantities.

In dog B., on the other hand, the faeces never had a bilious appearance, and analysis always showed either that bile was entirely absent or present only in very small quantities, while urobilin again was always present in abundance. These two animals therefore gave diametrically opposite results, and consequently the results yielded by the aromatic sulphates, together with what was found at the *post-mortem* examination, are of great interest; for by the estimation of the quantity of aromatic sulphates in the urine we are able to recognise the amount of intestinal putrefaction that is going on; and in dog A., as was found in other dogs without the large intestine, this was markedly diminished.

⁷ D. Gerhardt, Ueber Hydrobilirubin und seine Beziehungen zum Ikterus, *Inaug. Diss.*, Berlin, 1889.

Table showing the Nitrogen and Sulphate Output by the Urine in the Dogs after removal of their large Intestines. (Both Animals received daily 100 grammes of Lean Meat along with 100 grammes of Biscuit.)

	Days.	Weight of Dog in Kilos.	Total Nitrogen in Grammes.	Urine Sulphates.			
				Total.	Alkaline.	Aromatic.	Ratio.
Dog A. ...	1	4.05	4.427	0.619	A.	B.	A. : B.
	2	4.05	4.815	0.637	C.540	C.033	19 : 1
	3	4.05	4.120	0.555	C.518	C.037	14 : 1
Dog B. ...	1	5.30	4.508	0.509	C.149	C.059	7 : 1
	2	5.30	4.110	0.391	C.342	C.049	7 : 1
	3	5.30	4.461	0.416	C.364	C.051	7 : 1

In the above table are only given the results of three days' analysis in each of the dogs as a type; since the results on other days during which the experiments were continued were in each case similar. In the above two dogs both received exactly the same diet, so that in reality dog B. was receiving less food than dog A. per kilo. weight. However, the difference was small. In normal dogs fed on exactly the same diet the ratio of alkaline to aromatic sulphates I have frequently found to be from 9 to 1 to 8 to 1. In dog A., instead of the ratio of alkaline to aromatic sulphates being as normal, they were from 19 to 1 to 14 to 1, showing a marked decrease in the aromatic sulphates, and therefore pointing to decrease in the intestinal putrefaction. These results I have noticed in other dogs in which the large intestine has been removed. In dog B., although on exactly the same diet, the ratio of alkaline to aromatic sulphates was 7 to 1, pointing to an increased intestinal putrefaction.⁸ The cause of the intestinal putrefaction I am unable to give, but the dog was peculiar in many respects in the way its metabolism behaved, and was continually going off its food, although during the experiments above quoted it was on nitrogen equilibrium. As already stated dog A. passed in the feces only very little urobilin, while in dog B. almost the entire, or the entire bile, was converted into urobilin. Both dogs were killed, and the contents of the alimentary tract, as well as the walls of the intestine, were treated in exactly the same way as the normal animals above described. In dog A., below the entrance of the bile duct, the contents were bile stained, which lost their colour in the middle third of the small intestine. The contents remained colourless until just upon reaching the rectum, when they assumed a brownish-green colour, and just below the junction of the small intestine with the rectum, 4 cm. from the anus, they still retained a brownish-green colour with perchloride of mercury. No urobilin was present in the small intestine, and a very doubtful reaction in the contents of the rectum. The walls of the intestine throughout did not give any reaction with perchloride of mercury.

In dog B., in the first third of the small intestine the contents were green; the middle third was empty; the lower third showed green-coloured contents at its commencement—that is to say, about 70 cm. from the anus—and urobilin was present in the contents at 40 cm. from the anus. The contents of the rectum—6 cm.—contained large quantities of urobilin and a small quantity of biliverdin.

The fact that the analysis of the feces of dog A. showed more urobilin than was found in the contents at the *post-mortem* examination would be explained by the bacteria having longer time to act in reducing the bile pigment present.

Dog B., although found to be in sufficiently good health to gain in weight when properly fed, always had an excess of aromatic sulphates in its urine, and therefore increased intestinal putrefaction. In consequence of the increased intestinal putrefaction which extended up the small intestine, urobilin was formed even in the small intestine, and so much so that nearly all the bile pigment was converted into urobilin before it left the intestines.

⁸ The urine on standing deposited indigo blue as a precipitate.

The result obtained in this dog explains how in some human cases where there is increased intestinal putrefaction extending up the small intestine instead of as, under normal circumstances, commencing below the cæcum. The increased urobilin in the urine would thus seem not only to be a pathological sign of increased bile in the intestinal tract, as pointed out by Müller, but also significant of increased putrefaction in the intestine.

That intestinal bacteria are capable of converting bilirubin into urobilin has been long known, and is mentioned by Schmidt. In confirmation of the above results calomel gives us strong support. It is known that calomel, when given by the mouth, causes the feces to contain large quantities of bile pigment, and it has generally been put down as significant of the increased flow of bile into the intestine and increased peristalsis along the intestinal tract.

I have found in man that when small doses— $\frac{1}{2}$ gr. or so—of calomel are given at frequent intervals, the stools by degrees assume a green colour and contain large quantities of bile pigment and only small quantities of urobilin, and in these cases the calomel causes no purging. As we know, calomel diminished the aromatic sulphates in the urine, and therefore diminished the intestinal putrefaction. The green stool of calomel is in all probability partly due to increased bile, but chiefly to the diminution of intestinal bacteria, the biliverdin in consequence not being converted into urobilin.

Still further in support of the view that the increase of urobilin occurs in cases of increased intestinal putrefaction, I have found in one case since I obtained the above results, where there was a marked increase of aromatic sulphates there was also a great increase of urobilin. In fevers which are almost always accompanied by an increase of urobilin in the urine there is also an increase in the intestinal putrefaction; the same holds good for liver disease. In partial obstruction of the bile ducts the increased urobilin cannot be explained by increase of bile in the intestines, but seems to be the result of increased intestinal putrefaction. It would appear that the increase of urobilin in the urine is therefore not only of assistance in the diagnosis of diseases in which an increased destruction of blood corpuscles occurs, as stated by Müller and others, but also has significance in pointing to increased intestinal putrefaction.

In the case of dogs this does not hold good, for in none either examined by myself or by Dr. Putnam while working in my laboratory have we been able to discover any urobilin in the urine by any of the methods at present employed for its isolation or recognition. That dog's urine contains no urobilin has been already pointed out by A. Beck⁹ and Müller.

CONCLUSIONS.

1. That bile pigment present in the upper part of the small intestine during its passage along the alimentary canal is converted into some colourless chromogen, to be again converted in the lower part of the small intestine into bile pigment.

2. Urobilin is, as a rule, formed in the large intestine below the ileo-cæcal valve, and only rarely in the small intestine; that is to say, only in those parts where intestinal putrefaction is most active.

3. The staining of the wall of the cæcum and large intestine with urobilin is due to *post-mortem* diffusion, and is not any indication of the absorption of urobilin in the living animal. Why it should in some cases be most marked in the cæcum and just below the cæcum, and not in the rectum, can only be explained by the fact that those parts are generally found in the *post-mortem* room more decomposed than the rectum.

4. The increase of urobilin in the urine, as well as having pathological significance—as has been already recognised in cases of internal haemorrhages, such as cerebral, peritoneal, or hemorrhagic infarctions and extrauterine pregnancy, and probably when red blood corpuscles are being destroyed, as in infectious fevers, scurvy, and pernicious anaemia—points also in favour of increased intestinal putrefaction, and may be a useful chemical test for such purpose.

⁹ T. A. Beck, *Wien. klin. Woch.*, August, 1895, p. 617.

THE ACTION OF LYSIDINE AND PIPERAZINE AS URIC ACID SOLVENTS.¹

By F. WOODCOCK GOODBODY, M.D.

(From the Pathological Chemistry Department, University College.)
THE relative value of lysidine and piperazine as solvents of uric acid in the urine was investigated, as published opinions of their real use were so divergent. In the experiments performed up to the present the solvent power of these drugs has been tested on uric acid calculi or in patients. The mode of experimenting on patients leads to so many possible causes of error, such as changes in diet, mode of living, etc., that it is extremely hard to draw conclusions from them.

As is now well recognised, uric acid is not eliminated from the kidneys in the form of free uric acid, and never exists in the blood except as some more or less solvent urate. The experiments of Bence Jones and Sir William Roberts show that urates are in all probability excreted as quadruriurates in the urine.

The proper method of testing the value of these drugs therefore appeared to be to see what power they would have of retaining urates in solution in the urine. At the suggestion of Professor Vaughan Harley the following experiments were performed in his laboratory, and I must express my thanks to him for his kind assistance and advice throughout my research. The experiments were done on the urine of a person suffering from uric acid gravel, together with other symptoms, such as muscular and lumbar pains.

Throughout the experiment the patient was kept on the same diet, and the amount of fluid was kept as nearly as possible equal. During the experiments on the action of piperazine taken internally the amount of exercise was kept equal. In all cases the urine for twenty-four hours was collected, and in every case the urine on standing deposited urates.

The total daily nitrogen was estimated by Kjeldahl's method, so as to control the diet and ensure that the patient remained on nitrogen equilibrium. The quantity of uric acid was estimated by Ludwig-Salkowski's and Gowland-Hopkins's methods, and in all cases two analyses were made, and the results rejected unless the difference showed no cause of error. The acidity was regularly estimated by titration with 10 normal sodium hydrate, and phenol-phthalein was used as an indicator. In the tables the acidity is expressed as grammes of solid sodium hydrate per cent. of urine.

PIPERAZINE.

The experiments on piperazine can be divided into two groups: (a) Piperazine artificially added to urine tending to deposit urates. To two specimens of 220 c.cm. of urine piperazine was added, in one case 0.1 g., and in the other 0.2 g., and one specimen of the same urine was allowed to stand as a control. After a given number of hours two samples of each were treated in precisely the same manner, namely, filtered, and the quantity of uric acid in the filtrate estimated. The acidity present was also estimated in the filtrate. By this means one was able to see how much uric acid had been prevented from being precipitated, and it was thus hoped to test the solvent power of piperazine in a better manner than by employing uric acid, which had already been precipitated from the urine, and was no longer in the form in which it was originally in solution in the organism.

In the urine that stood twenty-four hours the average of the two cases to which piperazine was not added yields only 0.051 g. per cent. uric acid retained in solution, while the urine to which 0.1 g. piperazine was added kept 0.061 g. per cent. in solution.

The acidity rose from 0.41 to 0.44 g. of sodium hydrate per cent. on the addition of 0.1 g. piperazine.

Of the two specimens which stood thirty-six hours one contained 0.051 g. per cent. of uric acid, while in the other 0.061 g. per cent. was kept in solution by the addition of 0.1 g. piperazine, while the acidity was only increased from 0.39 g. to 0.40 g. of sodium hydrate per cent.

It is thus seen that piperazine when added to the urine

after having passed caused a considerable inhibitory action in preventing the precipitation of uric acid, even as long as thirty-six hours. That all was not kept in solution may be due either to insufficient solvent power, or that the urates which had been precipitated during the twenty-four hours' collecting of the urine were not redissolved.

TABLE I.—Showing the Result of the Addition of 0.1 g. of Piperazine to 220 c.cm. of Urine.

Day.	Quantity.	Specific Gravity.	Nitrogen, Total.	Total.	Per Cent.	Time Stood before Filtering, in hours.	Filtered Urine.		
							Uric Acid in Day's Urine.	Normal Urine.	Urine and 0.1 g. Piperazine.
1	900	1030	19.46	—	—	24	0.050	0.41	0.064 0.40
2	1160	1023	17.92	—	—	24	0.042	0.41	0.057 0.47
Average	1030	1027	18.69	—	—	24	0.051	0.41	0.061 0.44
3	1180	1033	18.50	0.91	0.077	36	0.051	0.39	0.061 0.40

TABLE II.—Showing the Effect of the Addition of 0.2 g. Piperazine to 220 c.cm. Urine.

Day.	Quantity.	Specific Gravity.	Nitrogen, Total.	Total.	Per Cent.	Time Stood before Filtering, in hours.	Filtered Urine.		
							Uric Acid in Day's Urine.	Normal Urine.	Urine and 0.2 g. Piperazine.
1	900	1030	19.46	—	—	24	0.059	0.41	0.068 0.05
2	1160	1023	17.92	—	—	24	0.042	0.41	0.064 0.39
3	1091	1027	18.89	0.99	0.092	24	0.063	0.51	0.064 0.40
4	1300	1022	—	1.09	0.084	24	0.068	0.38	0.073 0.38
5	1620	1020	18.33	1.11	0.069	24	0.058	0.24	0.065 0.23
Average	1214	1024	18.65	1.06	0.082	24	0.058	0.39	0.067 0.38

The urine on an average contained no less than 1.06 g. of uric acid per diem, or 0.082 per cent. The average of the 5 cases to which piperazine was not added to the urine was, after twenty-four hours' standing, 0.058 g. per cent. of uric acid retained in solution, while 0.067 g. per cent. of uric acid was found in those to which 0.2 g. piperazine was added. The acidity was reduced from 0.39 g. of sodium hydrate per cent. to 0.38 g. by the addition of 0.2 g. piperazine.

(b) Piperazine given internally in a case tending to deposit urates: For four days no drug was given in order to see the quantity of urine passed, and the quantity of uric acid and nitrogen eliminated and also the acidity were comparatively constant. During nine days 1 g. of piperazine was administered in three doses each day, and during the next five days 2 g. of piperazine was administered daily. Throughout the diet and fluids were kept the same.

The quantity of urine is seen to have been increased from 1103 c.cm. to 1476 c.cm. by 1 g. piperazine daily. This increase was most marked during the first five days, rising on one occasion to as much as 2197 c.cm., nearly double that on any normal day. The increase of the dose of piperazine to 2 g. per diem caused a further increase of the average daily amount of urine to 1680 c.cm., so that piperazine had an undoubted diuretic action, which was again most marked at the commencement. The diuretic action was probably not kept at its height from no increase of fluids being allowed. The total

¹ Towards the expenses of this research a grant was made by the British Medical Association on the recommendation of the Scientific Grants Committee of the Association.

TABLE III.—Showing the Effect of Piperazine Taken Internally on the Quantity of Urine, Uric Acid, etc.

Day.	Quantity.	Specific Gravity.	Nitrogen.	Nitrogen as Uric Acid.	Uric Acid.			Acidity of Urine in Solid NaOH.	Remarks.
					Total.	In Filtrate.	In Sediment.		
1	c.c.m. 1180	103	Total 18.50	0.30	0.91	p. c.	p. c.	p. c. 0.44	Normal.
2	1170	103	18.85	0.32	0.95	—	—	0.42	"
3	900	103	19.40	—	—	—	—	0.53	"
4	1160	102	17.92	—	—	—	—	—	"
Average.	1103	102	18.68	0.31	0.93	—	—	0.46	2 g. piperazine.
5	1001	102	18.89	0.33	0.99	0.069	0.0232	0.53	2 g. piperazine.
6	1360	102	—	0.30	1.09	0.069	0.0150	0.44	"
7	1620	102	18.33	0.37	1.11	0.058	0.0104	0.29	"
8	1530	102	20.08	0.35	1.06	0.067	0.0026	0.32	"
9	2197	101	20.15	0.32	0.95	0.033	0.0090	0.26	"
10	1100	102	18.79	0.33	0.98	0.073	0.0166	0.44	"
11	1610	102	19.44	0.34	1.01	—	—	0.30	"
12	1630	102	17.31	0.34	1.03	0.055	0.0098	0.27	"
13	1240	102	18.62	0.34	1.01	0.073	0.0091	—	"
Average.	1476	102	18.95	0.34	1.02	0.062	0.0121	0.36	2 g. piperazine.
14	2242	101	19.65	0.33	0.99	0.047	0.0091	0.23	2 g. piperazine.
15	1630	102	19.52	0.33	0.98	0.056	0.0011	0.23	"
16	1530	102	19.56	0.35	1.05	0.063	0.0041	0.33	"
17	1880	102	20.58	0.37	1.12	0.050	0.0056	0.31	"
18	1520	102	19.21	0.46	1.37	—	—	0.36	"
Average.	1680	102	19.74	0.37	1.10	0.056	0.0049	0.30	

nitrogen eliminated was during the normal days 18.68 g. per diem, and 1 g. piperazine increased its daily elimination to 18.95 g. This was more marked on the fourth and fifth days, while increasing the dose to 2 g. caused a further rise of the nitrogen eliminated to 19.7 g., most marked on the fourth day, when no less than 20.58 g. were excreted. This increased elimination of nitrogen is partly due to the increase of the nitrogen of the uric acid, as is shown in the column giving the amount of nitrogen eliminated as uric acid, which rose from 0.31 g. to 0.34 g. on 1 g. of piperazine, and then further to 0.37 g., while taking 2 g. piperazine. It is thus seen piperazine, besides having a diuretic action, stimulated nitrogen metabolism and caused an increase in the total nitrogen eliminated in the urine, which was only in part due to the increased excretion of uric acid by the kidneys, and probably in part due to its diuretic action, as we know the increase of fluids passing through the kidneys is always accompanied with an increased nitrogen elimination. The quantity of uric acid in the filtered urine was unfortunately not estimated during the normal days. During each day on which 1 g. piperazine was administered the filtered urine contained an average 0.062 g. per cent. of uric acid, while 0.0121 g. per cent. was precipitated. Increasing the dose of piperazine to 2 g. daily gave an average quantity of 0.056 g. per cent. of uric acid in the filtered urine, while only 0.0049 g. per cent. was precipitated. The quantity of uric acid was increased during the first four days that 1 g. piperazine was given; it then fell to almost normal, and finally rose again from no apparent cause. There was a further rise two days after the dose was doubled, which had not begun again to fall when the experiments were terminated. This increase of uric acid appeared to be due to the washing out from the tissues of urates by the better solvent power of the blood, as the experiments seem to show that piperazine causes no increased formation of uric acid in the organism. The fall during the continuance of the drug would thus be explained by most of the urates having been removed from the tissues.

The average acidity during the normal days was 0.46 g. per cent. sodium hydrate. This diminished on the administration of 1 g. piperazine to 0.36 g. per cent., and the doubling of the dose caused a further decline to 0.30 g. per cent. sodium hydrate. So piperazine also has the power of diminishing the acidity of the urine.

LYSIDINE.

In the investigation into the solvent power of lysidine pre-

cisely the same plan was followed as in the experiments with piperazine, namely:—

(a) The effect of the addition of lysidine to urine which had deposited urates was in every case to diminish the amount of the deposit, while there was at the same time a slight decrease in the amount of acidity.

Two series of experiments were performed to investigate the influence the addition of lysidine to the urine, both being carried out in the same manner—namely, two specimens of 220 c.cm. urine were taken, to one of which 0.2 g. lysidine was added, the other being used as a control.

These samples were allowed to stand for a certain time, after which they were filtered, and the uric acid and acidity estimated in the filtrate.

In the tables two series are given separate, as the total uric acid in these differed so markedly that they are better thus grouped.

TABLE IV.—Showing the Effect of the Addition of 0.2 g. Lysidine to 220 c.cm. Urine.

Day.	Quantity.	Specific Gravity.	Nitrogen, Total.	Uric Acid in Day's Urine.	Filtered Urine.		
					Total.	Per Cent.	Time stood before Filtering, in hours.
1	c.c.m. 1620	1020	19.38	1.07	0.066	24	0.059 0.35 0.061 0.32
2	1210	1032	19.59	1.21	0.099	24	0.077 0.41 0.084 0.40
3	1800	1024	19.33	0.98	0.056	24	0.042 0.28 0.050 0.26
Average	1536	1025	19.43	1.08	0.074	24	0.059 0.35 0.065 0.33

In the above series of experiments the normal urine contained on the average 0.059 g. per cent. in the filtrate, while the urine, to which 0.2 g. lysidine was added kept 0.065 g. per cent. in solution. The acidity showed a decrease on the addition of 0.2 g. lysidine from 0.35 g. per cent. to 0.33 g. per cent. of sodium hydrate.

TABLE V.—Showing the Effect of the Addition of 0.2 g. Lysidine to 220 c.cm. Urine.

Day.	Quantity.	Specific Gravity.	Nitrogen, Total.	Uric Acid in Day's Urine.	Filtered Urine.		
					Total.	Per Cent.	Time stood before Filtering, in hours.
1	c.c.m. 1380	1027	19.26	0.91	0.066	24	0.059 0.29
2	1870	1020	19.89	0.69	0.037	24	0.029 0.22
3	1610	1021	20.79	0.86	0.053	24	0.039 0.29
Average	1620	1023	19.98	0.82	0.052	24	0.042 0.27

In this case the average amount of uric acid contained in the filtrate of the normal urine was 0.042 g. per cent., while in the filtrate of the urine to which lysidine was added, 0.049 g. per cent. was found, showing an average increase of 0.014 g. per cent. of uric acid retained in solution. Unfortunately, the total quantity of uric acid during these experiments with lysidine cannot be compared with similar experiments when piperazine was used, as the total quantity in the urine was not the same. Lysidine, however, had an undoubted power of keeping urates in solution.

(b) Lysidine taken internally in a case showing a tendency to deposit urates.

For four days no drug was taken in order to estimate the quantity of urine passed, the quantity of uric acid and nitrogen eliminated, and the amount of acidity per cent. Then for eight days 1 g. lysidine was taken in two doses each day, and during four days 2 g. lysidine daily. Throughout the experiments the diet and fluids were kept precisely the same as during the piperazine experiments. The exercise was also kept about the same.

TABLE VI.—*Showing the Effect of the Internal Administration of Lysidine.*

Day.	Quantity. c.cm.	Specific Gravity.	Nitrogen.	Nitrogen as Uric Acid.	Uric Acid.			Acidity in Grammes of Solid NaOH.	Remarks.
					Total	Total	Unfiltered Urine.		
1	1380	1027	19.46	0.30	0.91	0.58	0.0070	0.32	Normal.
2	1370	1020	19.88	0.23	0.69	0.30	0.0067	0.22	"
3	2074	1019	19.85	0.19	0.58	0.26	0.0022	0.24	"
4	1990	1019	19.22	0.24	0.72	0.35	0.0013	0.21	"
Average.	1829	1021	19.56	0.24	0.73	0.37	0.0043	0.25	
5	1510	1022	19.36	0.27	0.82	0.39	0.0150	0.29	1 g. lysidine.
6	1530	1023	19.99	0.28	0.85	0.46	0.0093	0.33	" "
7	1590	1025	20.21	0.32	0.95	0.43	0.0139	0.29	" "
8	1490	1025	21.69	0.34	1.02	0.55	0.0135	0.31	" "
Average.	1530	1024	20.35	0.30	0.91	0.46	0.0129	0.31	
9	1680	1025	21.16	0.26	0.78	0.43	0.0039	0.29	" "
10	2230	1017	20.41	0.21	0.63	0.27	0.0004	0.22	" "
11	1750	1021	19.16	0.26	0.78	—	—	0.23	" "
12	1630	1022	19.88	0.26	0.77	0.38	0.0092	0.28	" "
Average.	1823	1021	20.15	0.25	0.74	0.36	0.0045	0.26	
13	1680	1024	22.52	0.28	0.85	0.49	0.0019	0.29	2 g. lysidine.
14	1879	1021	22.28	0.21	0.64	0.31	0.0050	0.23	" "
15	2440	1016	23.86	0.23	0.69	0.25	0.0028	0.20	" "
16	2191	1017	22.11	0.24	0.72	0.34	0.0015	0.26	" "
Average.	2045	1019	22.69	0.24	0.72	0.35	0.0029	0.25	

The average daily quantity of the urine fell from 1829 c.cm. to 1530 c.cm. during the first four days of the administration of 1 g. lysidine; this increased to 1823 c.cm. during the next four days, and, on doubling the daily dose, the secretion of the urine rose to 2045 c.cm. The exceptionally high excretion of urine during the normal days can only be explained by some nervous excitement. As a rule the quantity was much less. Lysidine appears to have even a greater diuretic action than piperazine.

The average elimination of nitrogen rose from 19.56 g. to 20.35 g. during the first four days of the administration of the lysidine, and fell during the next four days to 20.15 g., rising to 22.69 g. on increasing the dose. The quantity of nitrogen eliminated as uric acid increased from 0.24 g. to 0.30 g. during the first period of giving lysidine. During the next period it fell to 0.25 g., and still further sank to 0.24 g. on doubling the daily dose.

The quantity of uric acid in the filtered urine averaged 0.037 g. per cent. during the normal days, and that in the sediment averaged 0.0043 g. per cent. During the first period in which lysidine was given the quantity in the filtered urine rose to 0.046 g. per cent., and in the sediment to 0.0129 g. per cent., but fell in the next period to 0.036 g. per cent. in the filtered urine, and to 0.0045 g. per cent. in the sediment.

When the dose was doubled the quantity of uric acid in the filtered urine fell to 0.035 g. per cent., and to 0.0029 g. per cent. in the sediment.

The total quantity of uric acid was increased by 0.18 g. during the first period of the administration of lysidine, particularly on the third and fourth days. It then reached the maximum (1.02 g.), and fell in the next twenty-four hours to 0.78 g. In the next period the average excretion was 0.01 g. above that of the normal standard. On the first day on which the dose was increased the quantity of uric acid rose 0.11 g. above the average excretion of the second period of the administration of 1 g. lysidine, but was less than during the first period, and only 0.12 g. more than the normal. It fell in the

next twenty-four hours, and thus showed an average decrease of 0.02 g. below the previous four days and of 0.01 g. below the normal standard. Lysidine would appear from these experiments to wash out the urates from the tissues even in a better way than piperazine, and also to hold a greater quantity of uric acid in solution.

During the administration of 1 g. lysidine the acidity in the first period showed an increase of from 0.25 g. per cent. to 0.31 g. per cent. sodium hydrate; in the next period it diminished to 0.26 g. per cent., and still further sank to 0.25 g. per cent. sodium hydrate when the dose was doubled.

In this paper I have not discussed in any way the results obtained by other observers, such as Gordon, Fawcett, Medelsohn, Grawitz, Schmidt, and Biesenthal, etc., as this would lead to too lengthy a paper, and I thought it would be better here merely to quote my own results and leave for some future occasion a full discussion of this most important subject.

The conclusions to be drawn from this vexed question are: Piperazine and lysidine, when added to a urine tending to deposit uric acid gravel, are capable of hindering the deposit during standing.

The total experiments, all of which are unable, from want of space, to be given here, show that lysidine is a more powerful solvent for uric acid than piperazine.

Both piperazine and lysidine when taken internally appear to increase the elimination of uric acid, not by increasing its formation in the organism, but by rendering the blood more capable of removing it from the tissues by increasing its solvent power. So that prolonged administration of these drugs in the end causes a diminution in the quantity of uric acid eliminated by the kidneys.

Piperazine and lysidine are both diuretics, and cause an increased elimination of nitrogen, which is partly due to the increase of the nitrogen in the uric acid and in part due to its diuretic action.

A DISCUSSION ON THE PATHOLOGY OF COAL GAS POISONING.

I.—JOHN HALDANE, M.A., M.D.,

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It is well known that coal gas, even when largely diluted with air, is poisonous, and as carbonic oxide is the only known markedly poisonous constituent of purified coal gas, the symptoms produced are usually attributed to carbonic oxide. The cherry-red appearance, characteristic of carbon monoxide poisoning, has also frequently been described in cases of coal gas poisoning. Nevertheless, we can hardly assume without further evidence that all the symptoms are due to carbon monoxide. Coal gas contains about 80 per cent. or more of hydrogen and marsh gas. The former of these is well known to be a physiologically indifferent gas. The same is true of the latter, although the statement has found its way into some books that marsh gas is somewhat poisonous. I have myself breathed for some time without feeling the slightest effects a mixture of 80 per cent. of marsh gas and 20 per cent. of oxygen, and an animal kept in the same mixture remained quite unaffected. As to the action of some of the other hydrocarbons or other substances present in small quantities in coal gas there is room for doubt, hence I thought it worth while to make a few experiments on this subject. It will, however, be more convenient if I return to these later and meanwhile assume provisionally that carbonic oxide is practically the only really poisonous substance in coal gas.

The intensely poisonous action of carbonic oxide, and the property which it possesses of combining with the haemoglobin of the blood to the exclusion of oxygen have been known for long. Until recently, however, there remained a doubt as to whether its action on the blood was really the key to the whole of the poisonous action of carbonic oxide. Some of the latest writers on the subject have, indeed, concluded that it acts as an intense poison, apart altogether from its influence in excluding oxygen from the blood. As a knowledge of its

mode of action is essential to an understanding of the pathology of coal gas poisoning, it will not be out of place if I endeavour to shortly summarise the observations which have led me to conclude¹ that its property of excluding oxygen from the haemoglobin of the blood really affords a complete explanation of its poisonous action, so that the latter may be referred solely to oxygen starvation.

The blood carries oxygen from the lungs to the tissues in two ways. There is first of all the oxygen in loose chemical combination with the haemoglobin, and, secondly, the oxygen in simple solution. The venous blood (assuming that it already contains about 12 volumes per cent. of oxygen) probably takes up normally in the lungs about 8 volumes per cent. of oxygen in chemical combination and $\frac{1}{2}$ a volume per cent. in simple solution. The amount taken up in simple solution is not enough to support life, hence if the haemoglobin is paralysed by carbonic oxide death must ensue. But as the amount taken up in simple solution varies as the partial pressure of the oxygen in the atmosphere, we can by increasing the pressure of the oxygen so increase the amount of oxygen taken up by the blood in simple solution as to make the animal independent altogether of its red blood corpuscles as oxygen carriers. Hence, if carbonic oxide acts only by diminishing the oxygen supply to the blood its poisonous action should be abolished in presence of oxygen at sufficiently high pressure. Now, I found by experiment that in presence of oxygen at two atmospheres' pressure the poisonous action of carbonic oxide was abolished, although haemoglobin exposed to the same atmosphere and pressure became at once saturated with carbonic oxide. At two atmospheres' pressure the blood of a living animal would take up about 5 per cent. by volume of oxygen, and this amount was therefore sufficient to sustain life. The apparatus on the table was used in this experiment. The thick-walled jar shown is first filled with pure oxygen, a mouse put in, and the perforated cork firmly closed by means of a screw clamp. More oxygen is then driven in from the oxygen cylinder until the mercury gauge indicates a pressure of 30 inches (or two atmospheres, including atmospheric pressure). By then directing the pressure from the oxygen cylinder in another direction water is driven into a jar of carbonic oxide and the gas thus forced into the jar containing the animal until the gauge stands at 60 inches, indicating that the animal is exposed to a mixture containing carbonic oxide exercising one atmosphere's pressure, besides oxygen exercising two atmospheres' pressure. Although it becomes somewhat short of breath the mouse continues to live and walk about in the jar. As soon, however, as the pressure is lowered death ensues, as the amount of dissolved oxygen then becomes insufficient to support life. This experiment seems to establish beyond all doubt the theory that carbonic oxide acts as a poison simply by depriving the tissues of oxygen, and that any other mode of action which it may possess is at any rate so slight as to be absolutely negligible.

If carbonic oxide acts simply by combining with haemoglobin and depriving the tissues of oxygen it ought to have little or no action on animals without haemoglobin, and the next experiment shows that this is the case. The two bottles shown contain, one a mixture of about 75 per cent. of carbonic acid and 25 per cent. of oxygen, the other about 75 per cent. of carbonic oxide and 25 per cent. of oxygen. You will see that the beetle (*blatta orientalis*) in the bottle containing carbonic oxide, where it has been for three days, continues to live and shows no signs of discomfort, while that dropped into the carbonic acid becomes motionless within about thirty seconds. This experiment illustrates well the fact that while carbonic acid is what one might call a direct protoplasmic poison, carbonic oxide is not.

A further interesting point about the carbonic acid mixture, which would be intensely poisonous to any animal or plant, is that it supports combustion, as now shown. Carbonic acid has very little specific action in extinguishing lights, and the statements often made on this subject are very misleading.

The three bottles now shown contain blood saturated with oxygen (bright scarlet) blood, completely deprived of oxygen by the action of bacteria (dark purple), and blood saturated with carbonic oxide (bright scarlet). The blood saturated

with carbonic oxide has, when examined in bulk, precisely the same colour as the blood saturated with oxygen. In a very thin layer, however, the carbonic oxide blood is pink, while the oxygenated blood is yellowish red. By far the best way of recognising the presence of carbonic oxide in blood is to dilute a drop of the blood to $\frac{1}{10}$ th or more with water, as in narrow test tubes of equal diameter, with a solution of normal blood diluted until the depth of colour is about equal. The carbonic oxide blood appears pinker; and if part of the same solution be shaken for a minute or two with coal gas, so as to saturate it with carbonic oxide, and placed in a third test tube, it is easy to make a rough estimate of the percentage to which the blood under examination is saturated. A more accurate colorimetric method is described in a paper which I recently published in the *Journal of Physiology*.²

It used at one time to be believed that carbonic oxide could not be driven out again from haemoglobin. This belief has for long been known to be erroneous. The affinity of carbonic oxide is (in the dark) about 230 times as powerful as that of oxygen for haemoglobin. Oxygen has, nevertheless, a marked influence in driving out, or keeping out, carbonic oxide from haemoglobin. The greater the percentage or partial pressure of the oxygen in any given atmosphere the less is the effect on haemoglobin of a given percentage of carbonic oxide. When blood or haemoglobin solution is shaken up with air containing about 0.09 per cent. of carbonic oxide the haemoglobin becomes equally saturated with oxygen and carbonic oxide. To obtain the same result with a mixture of carbonic oxide and pure oxygen nearly five times as much carbonic oxide is necessary, since there is nearly five times as much oxygen in the pure oxygen as in air. The same law applies to the action of carbonic oxide on animals or men. In an atmosphere of pure oxygen carbonic oxide is actually far less poisonous than in air; and a diminution in the oxygen percentage of air renders carbonic oxide more poisonous. Moreover the breathing of pure oxygen drives out carbonic oxide from the blood of a patient suffering from carbonic oxide poisoning five times as fast as air would do.

In breathing carbonic oxide experimentally no unusual effects are felt during rest until the blood is about 30 per cent. saturated, but any exertion causes dizziness, loss of power, and shortness of breath. These symptoms, occurring on exertion, are the first signs of carbonic oxide poisoning. With the blood more than 30 per cent. saturated throbbing of the vessels of the neck, palpitations, and slight shortness of breath are felt even during rest. As the saturation of the blood increases the power of movement becomes more and impaired, and the senses are also affected. At 50 per cent. saturation I found it scarcely possible to stand, but otherwise there was no positive discomfort. These symptoms are the same as balloonists and mountain travellers experience at high altitudes, and are undoubtedly due simply to want of oxygen. One symptom occasionally observed at high altitudes has also been recently described³ as sometimes produced by afterdamp (which contains carbonic oxide) after explosions in coal mines. This is exhilaration or excitement. Most persons exposed to carbonic oxide seem, however, to feel rather drowsy and torpid.

In the course of a recent inquiry⁴ on the causes of death in colliery explosions I examined the bodies of 120 of the men killed in the three great colliery explosions which have occurred since January. It turned out that in nearly every case death was due to carbonic oxide poisoning, and that the symptoms of the survivors and rescuers were also due to this gas. Unfortunately it was not possible to make *post-mortem* examinations, except on the horses, but I determined the percentage saturation with carbonic oxide of the blood from the external jugular vein in a number of bodies, besides carefully noting the very characteristic external appearances. As regards external appearances three classes of cases may be distinguished. 1. Those of men who had apparently died slowly in air containing a small percentage of carbonic oxide. 2. Those who had apparently died more rapidly in air or gas containing a larger percentage. 3. Those who had probably

¹ Loc. cit., p. 433.

² Davis, *Transactions South Wales Institute of Mining Engineers*, 1896.
⁴ Report to the Secretary of State on the Causes of Death in Colliery Explosions, 1896.

actually died in fresh or non-poisonous air from the after-effects of carbonic oxide.

In the first class of cases, which was by far the most numerous, the bodies, where not disfigured by coal dust or superficial burns, often presented an extraordinarily life-like appearance. The amount of colour visible in the lips, skin, etc., varied much in different cases, but this colour was always a more or less natural looking pink. In a few cases the lips and skin were so pale that very careful examination was necessary in order to determine the cause of death. The venous blood in several examples examined was found to be from 79 to 83 per cent. saturated with carbonic oxide. The first sample handed round is from one of these cases. For purposes of comparison some normal blood has been placed in a second tube, similarly sealed up some time ago and left. In a third tube some of the same normal blood, freshly sealed up with air, has been placed. In this third tube oxygen is still present, while every trace of oxygen has, of course, disappeared from the contents of the other tubes. Putrefaction has caused the solution of the corpuscles in all three tubes, and this gives the samples a very dark colour, except when seen in a thin layer on the sides of the tubes. On examining a thin layer of the blood the contrast between the samples in the three tubes is very striking. The miner's blood has a cherry red colour, in striking contrast with the bluish purple of the second tube and the yellowish red of the third.

The three test tubes now shown contain: No. 1, some of the miner's blood diluted to about $\frac{1}{10}$ th. No. 2, normal blood similarly diluted; and, No. 3, some of the same solution of normal blood saturated with carbonic oxide. One can easily see by the colour that the miner's blood is about 80 per cent. saturated with carbonic oxide. On examining the undiluted miner's blood with one of the spectroscopes you will notice the double band indicating the presence of carbon monoxide, while the (reduced) normal blood gives only a single band. The spectroscopic test is, however, not nearly so delicate as the simple colour test just described, and becomes useless when the blood is less than 40 per cent. saturated.

In the second class of cases, which was far less common, there was marked flushing of the capillaries and veins of the face and neck with bluish-red blood. The superficial veins on the front of the chest were distended so as to form a prominent network. The venous blood was 63 per cent. saturated in one of these cases. The cyanosed appearance corresponds to that observed in acute or subacute suffocation from want of oxygen, and seems to indicate that death had been pretty rapid.

In the third class of cases, which includes those who died after being brought out alive, the appearances of the bodies were not characteristic, and carbonic oxide might have entirely disappeared from the blood, so that the cause of death could only be inferred from the history of the case. Some of the horses examined belonged to this class. In one, which died 15 hours after being found, no trace of carbonic oxide was present in the blood. In another which had died in a stable, the blood was only 20 per cent. saturated. In some of the other horses lying near in the same stable the blood was much more highly saturated.

From experiments on myself I estimated that it would probably require about 6 hours for the blood of a man nearly poisoned by carbonic oxide to completely free itself from the gas. Most of the carbonic oxide would be got rid of in a much shorter time however.

When an animal is placed in an atmosphere containing more than 2 or 3 per cent. of carbonic oxide it dies before the venous blood has time to become more than partially saturated with the gas. With about 7 per cent. of carbonic oxide I found the venous blood only about 30 per cent. saturated, and carbonic oxide could not be detected by the spectroscope test. This must be borne in mind in the *post-mortem* examination of cases of suspected acute carbonic oxide or coal gas poisoning. None of the miners' bodies suggested poisoning of such acute character.

The after-symptoms of carbonic oxide poisoning remain for long after the gas has been eliminated from the body. In slight cases nothing but severe headache or nausea is felt; but in severe cases distinct consciousness may never return,

and death may even occur after a week or more. Recovery or partial recovery is often accompanied by symptoms which resemble in many ways those of strychnine poisoning.

From laboratory experiments on animals I found that 0.2 per cent. is about the minimum percentage capable of causing death within a few hours. About 0.05 per cent. causes slight symptoms in man after about an hour and a half. With smaller percentages the blood never becomes as much as 30 per cent. saturated, however long the inhalation is continued, since after about an hour and a half absorption ceases.

For the detection of carbon monoxide in air all that is necessary is to place in a dry and clean bottle about 5 c.cm. of a dilute blood solution (blood diluted to about $\frac{1}{10}$ th), and then after sucking some of the suspected air through the bottle, to cork it up and shake it for 10 minutes. During the shaking the bottle should be protected from light, which has a most powerful dissociating action on carbonic oxide haemoglobin. On pouring out the solution into a test tube and comparing its tint with that of some of the original solution in a similar test tube the presence of carbonic oxide is indicated by the pink tint of the first solution. The test becomes a quantitative one if the degree of pinkness of the blood solution, as compared with that of some of the same solution when saturated with coal gas, be estimated. With 0.09 per cent. of carbonic oxide in the air the haemoglobin will be half-saturated with carbonic oxide. The bottle shown is provided with a doubly tubulated stopper for more conveniently carrying out this test, and the saturation may be accurately estimated colorimetrically with the aid of standard carmine solution (also shown); 0.01 per cent. of carbonic oxide in air may easily be detected by this method. Blood solution was long ago recommended by Vogel as a qualitative test for carbonic oxide in air. He, however, used the spectroscope for the detection of carbonic oxide haemoglobin, and did not recognise the influence of light on the reaction. With these disadvantages the smallest proportion of carbonic oxide which he could detect was 0.2 per cent.

I must now refer to the question whether any other poisonous substances existing in coal gas co-operate with carbonic oxide in producing the symptoms of poisoning. To obtain an answer to this question I have used the methods already referred to of depriving the carbonic oxide of its poisonous action. The bottle now shown is filled with oxygen mixed with $3\frac{1}{2}$ per cent. of coal gas. This percentage (equal to 0.5 per cent. of carbonic oxide for Oxford coal gas) in air suffices to cause death in a mouse. You will see, however, that in the oxygen a mouse remains quite unaffected. The oxygen neutralises the action of the carbonic oxide, and no other substance in the coal gas has any effect. Hence, if any poisonous substance be present, its action is negligible as compared with that of the carbonic oxide.

On putting a mouse in oxygen at two atmospheres' pressure, and then driving in coal gas to a total pressure of three atmospheres, the animal continued for some time to live and move about, but it was more affected than when the corresponding experiment was made with carbonic oxide. Some more or less toxic substance other than carbonic oxide seemed to be present in the coal gas in sufficient amount to produce symptoms when a very large proportion of coal gas was present. A beetle placed in an atmosphere of 80 per cent. of coal gas and 20 per cent. of oxygen was distinctly affected after a few minutes, and seemed to lose the power of co-ordinating its movements. The same animal soon revived in the fresh air, and was afterwards put into a bottle containing 80 per cent. of carbonic oxide and 20 per cent. of oxygen, in which it remained unaffected. The conclusion from all these experiments is that while coal gas does contain other deleterious substances besides carbonic oxide, their action is of no importance whatever as compared with that of the carbonic oxide, and may be altogether neglected.

Before concluding my paper, I should like to refer to a matter which seems to me to call for close public attention. I recently had occasion to make for experimental purposes one or two determinations of the percentage of carbonic oxide in coal-gas. Expecting to find about five or six per cent. of carbonic oxide, I was not a little astonished to find in one sample 18 per cent., and in another sample 22 per cent. Several friends have since then sent samples from different

towns, and we are making a series of determinations in order to get some idea of the sort of mixtures which the various gas companies throughout the kingdom are now supplying. It is evident that in many towns the coal gas, or mixture of coal gas and water gas, now supplied is three or four times as poisonous as it was said to be in former times; 1 per cent. of gas containing 20 per cent. of carbonic oxide would suffice to cause death, and $\frac{1}{2}$ per cent. would cause complete helplessness. It is a matter for very serious consideration whether legislative restrictions should not be placed on the public supply of lighting gas containing more than a certain moderate percentage of carbonic oxide.

II.—JOHN R. DAVISON, M.D.,
Belfast

A CASE OF POISONING BY COAL GAS.

THE theory of the older physiologists that carboxyhaemoglobin was of such a stable character as to be practically incapable of dissociation, led to erroneous views as to the cause of the symptoms observed in carbon monoxide poisoning, and at the same time exerted a paralysing effect upon all efforts at treatment of such cases. Recently, however, some valuable work upon this subject has emanated from the Oxford laboratory. Dr. Haldane has shown¹, first, that carbon monoxide, apart from its action upon haemoglobin, is a physiologically inert gas, and that the symptoms it gives rise to are due not to any positive action upon the tissues, but simply to its negative action in depriving them of their oxygen; and, secondly,² that the stability of carboxyhaemoglobin is in inverse proportion to the tension of the oxygen in the alveoli. These two propositions being established, the whole aspect of these cases is changed; we put a different interpretation upon the symptoms, and we approach their treatment with more confidence and with some pretensions to scientific exactitude. Further, Haldane has introduced a colorimetric method for estimating the percentage saturation of blood with carbon monoxide, and he has proved by his experiments³ that symptoms are in direct proportion to the amount of carbon monoxide absorbed by the haemoglobin. This being so, even at the present time, an examination of the blood will enable us to form an opinion as to whether we may expect serious consequences or not, and eventually, after a series of cases has been recorded, it will prove a fairly accurate guide not only as to the ultimate prognosis, but also as to the sequælae we may anticipate and as a consequence the treatment we should adopt. Therefore, if we are to make any advance in our prognosis and treatment of cases of carbon monoxide poisoning, it will be not only necessary to accurately and minutely record every sign and symptom, but also to determine at frequent intervals the percentage saturation of the blood with carbon monoxide. It is not every physician, however, who has the apparatus or the skill to perform accurately the necessary examination; but any physician may procure a sample of the blood by pricking the finger of the patient and filling a capillary tube in the same way that lymph is obtained from a vaccine vesicle. These samples should be taken every half-hour, labelled, and submitted as soon as possible to a competent physiologist.

Unfortunately, the case reported below was observed before Haldane's method was published. The percentage saturation of the blood was not determined, and as a consequence the case loses a great deal of its scientific value and becomes simply a record of an exceptional termination to an otherwise severe case of coal gas poisoning.

On November 3rd, 1895, at 8.30 A.M. I was called to see K. M., who was said to be suffering from the effects of poisoning by coal gas. The girl had retired at 9 P.M. on the previous evening. Observing her absence in the morning the mistress went to her room about 8 o'clock, and on entering was met by a strong smell of gas. She found the girl lying on her right side, breathing heavily, but looking quite naturally. She was immediately removed to another room. She was a robust country girl, aged twenty-six, single, of strong build, and weighing about 12 stone. On arrival I found her propped up in a sitting posture unconscious. She was pale, slightly livid, breathing stertorously, and frothing at the mouth. Her ex-

tremities were exposed and cold, body warm, eyelids closed, pupils slightly but not markedly dilated, corneaæ insensitive, jaws clenched, extremities relaxed.

Having placed her in the recumbent position with pillows under the shoulders, I commenced artificial respiration, ordered hot jar to the feet and warm wraps for the body. A cylinder of oxygen was obtained from a neighbouring house, and this gas was administered freely. Owing to the fact that the jaws were clenched, the mouthpiece of the inhaler was inserted through a gap in the teeth caused by the absence of the first right upper bicuspid. Later, as she breathed principally by her nose, the mouthpiece was passed up one of her nostrils. Shortly after the commencement of the administration of the oxygen the breathing greatly improved and became less stertorous though still noisy, owing to accumulation of mucus in the trachea and bronchial tubes. On auscultation loud bronchial *râles* were heard all over the chest. The heart was beating regularly, pulse 104, medium in strength.

At 10 A.M. Dr. Storey came to my assistance. The same treatment was continued. She was now beginning to resist artificial respiration by extending her arms rigidly. The corneaæ were slightly sensitive, and she could be so far roused as to be sensible to pain. She moaned when the inner surfaces of the arms were slapped and drew them away. In the afternoon she was so far recovered that we thought there was no further necessity for artificial respiration, though oxygen continued to be administered at intervals. She was removed to bed and we then noticed that urine had been passed involuntarily.

The respirations at this time were shallow and rapid, about 40 to the minute. Noisy breathing had in a great measure ceased, though bronchial *râles* could still be heard on auscultation. Jaws were relaxing. Hot coffee was now obtained and carefully administered. At first she swallowed with difficulty and there seemed danger of the fluid passing into the respiratory passages. This was evidently due, not to paralysis of any of the muscles engaged in deglutition, but to want of sensibility in the palate and pharynx. The power of swallowing soon greatly improved, and before 11 P.M. a pint and a half of strong coffee had been administered. In the meantime there was considerable reaction. Pulse improved in strength, though still over 100. The face became flushed, and the skin began to perspire freely. On tickling her nose and slapping her arms she moved her head, opened her eyes, wrinkled her brows, and drew her arms away. When roused she took a long sighing inspiration, and then again subsided into short quick respirations. This was pretty much the condition of things at 11 P.M. We ordered a cup of strong coffee and a cup of hot milk alternately every two hours during the night. We then left with the expectation of finding our patient comparatively well in the morning. In the morning, however, our patient was in pretty much the same state—perhaps a little more easily roused. She was now removed to the infirmary.

For the following notes I am indebted to Drs. Hall and Gibson, under whose care she remained:

November 4th.—Patient unconscious, breathing stertorous, pupils dilated, pulse small and rapid, skin hot, face flushed, sonorous rhonchi all over chest, with heart sounds obscured. Arms rigid and flexed, eyes opened at times and then remained closed at long intervals. Can be roused and is sensible to pain.

November 5th.—Breathing better. Menstruating. Patient said "Let me alone" when battery was applied. Incontinence of urine. Temperature normal.

November 6th.—Rhonchi clearing up. Breathing good. Patient spoke again to-day when battery was applied. Temperature normal.

November 7th.—Morning: Much the same. Hypostatic congestion on the posterior surface of the body. Temperature normal. Evening: Crepitations all over chest. Breathing bronchial and rapid. Pulse 160 and weak. Temperature 105.4. Died at 2.50 a.m. November 8th from pneumonia, never having recovered complete consciousness.

In the above case we find as is usual in carbon monoxide poisoning the nervous symptoms predominating, though we have in addition certain respiratory symptoms that require consideration.

¹ *Journal of Physiology*, vol. XVIII, p. 450.

² *Journal of Physiology*, vol. XVIII, p. 462.

³ *Journal of Physiology*, vol. XVIII.

The frothing at the mouth and the bronchial *râles* were probably due to the irritating action of some of the constituents of coal gas (possibly sulphur compounds) producing excessive secretion of mucus in the mouth, trachea, and bronchial tubes. The hyperpnoea was more likely to be of nervous origin, the respiratory centre being stimulated to increased action owing to the defective supply of oxygen. The cause of the pneumonia, however, is more difficult of explanation. Prior to the onset of the rapidly fatal symptoms we find that the breathing had improved considerably as regards rapidity, the bronchial *râles* and rhonchi had disappeared, the temperature had remained normal, the reproductive organs had discharged their function, the nervous system was recovering its irritability, responding more readily to less powerful stimuli, and everything pointed to a gradual but satisfactory recovery. Under those circumstances I think we would hardly be justified in attributing the pneumonia to the direct effect of carbon monoxide. It seems to me that it was more probably of microbial origin, and if we accept the prevailing belief that we are always in the presence and possession of pneumonic organisms, we can readily understand that the cells of respiratory tract, owing to their exhausted condition, due in part to the deficient supply of oxygen and in part to the irritant effects of the coal gas, would make but a feeble resistance to the invasion of the pneumococcus.

It is the nervous symptoms, however, which predominate in cases of carbon monoxide poisoning. In the present instance they are of two kinds. First, those which indicate lessened nervous irritability, for example, loss of consciousness, general anaesthesia, insensibility of cornea, involuntary micturition, and complete relaxation of almost the whole of the muscular system; secondly, those which indicate increased nervous irritability such as hyperpnoea, tachycardia, and spasm of the levatores menti.

It is difficult to reconcile the contrary effects produced by deoxygenated blood upon different portions of nervous tissue. Though there is no satisfactory evidence that the passage of a nervous impulse along a nerve is the result of chemical changes, yet Foster⁴ says "We may infer that in nervous as in muscular substance a metabolism, of in the main an oxidative character, is the real cause of the development of nervous energy." If nervous tissue be supplied by blood gradually deprived of its oxygen, the complex chemical compound of an oxidative character, whose explosion gives rise to nervous energy, would gradually lose its oxygen, and consequently the nervous tissue would be incapable of generating nervous impulses, or in other words would lose its irritability. The loss of irritability in the nerve centres would be in inverse proportion to their stability. Therefore the highest centres, those connected with consciousness and the elaboration of mental processes would suffer first and suffer most. Hence amongst the first symptoms of carbon monoxide poisoning are, difficulty of perception, confusion of mind, and finally unconsciousness. In severe cases, some of the nerve cells may have been permanently injured, so that they never recover their irritability, and the patient always suffers from defective mental power. Unless in fatal cases, the centres for respiration, circulation, and deglutition retain their irritability, and being stimulated to increased action by the deoxygenated blood they give rise to hyperpnoea, tachycardia, and spasm of the levatores menti.

Again, if the supply of oxygen to the nervous tissues be suddenly cut off, before the complex chemical compound has had time to part with its oxygen, we would expect that all the nerve elements would be stimulated to increased action, and that this increased action on the part of the motor centres would be manifested by convulsive movements. Such a case has in fact been recorded by Dr. Scott.⁵

Prognosis.—The prognosis will depend on the percentage saturation of the blood with carbon monoxide.

Treatment.—The indications for immediate treatment are (1) asphyxia, (2) cardiac failure, (3) lowered body temperature. The treatment of the asphyxia will consist in the performance of artificial respiration, and the administration of oxygen. Other methods have been suggested for the removal of the carbon monoxide from the blood, such as venesection and

transfusion. These methods are based upon an erroneous idea as to the stability of carboxyhaemoglobin. Acting upon the supposition that carboxyhaemoglobin is practically incapable of dissociation, it is considered necessary that the carboxyhaemoglobin or a portion of it should be removed by venesection, and that a corresponding amount of oxyhaemoglobin should be restored to the circulation by transfusion. But, as already stated, Haldane has shown that the stability of carboxyhaemoglobin is in inverse proportion to the tension of the oxygen in the alveoli; therefore, all our efforts must be directed to increase the tension of the oxygen in the alveoli, and this can only be accomplished by artificial respiration and the administration of oxygen.

To overcome this cardiac failure it will be necessary to resort to stimulants. The question is what form of stimulant is the most suitable. I think both alcohol and ether are contraindicated as they lessen the oxidising power of the blood.⁶ Caffeine is the drug *par excellence* under these circumstances, and when combined with heat in the form of hot coffee it forms an ideal stimulant in cases of poisoning by carbon monoxide.

The lowered body temperature will be restored to its normal condition by means of external heat in the form of hot wraps, jars, baths, etc., and friction of the surface.

Such is the immediate treatment. And we find as a rule that in a few minutes to a few hours, according to the severity of the case, a marked reaction takes place, and all danger of syncope and asphyxia is past. Haldane⁷ says that in "cases of severe poisoning by carbonic oxide with the blood about 70 per cent. saturated, it would take about six or seven hours for the blood to return to a practically normal condition." But though we may have averted any immediate tendency to a fatal result, still there is considerable danger owing to the exhausted condition of the cells in different portions of the body. There is danger from microbial infection. The cells of the respiratory tract may be so exhausted that they are incapable of resisting the invasion of not only the pneumococcus (as in the above case) but any other organism which may chance to be present. Again, the cells of nerve centres from the highest to the lowest are profoundly affected. Even the most stable, the automatic centres, may become so disorganized as to be incapable of discharging their functions. The motor centres will, on slight provocation, run riot in the form of convulsions. And finally the highest centres may become delirious in their action and produce mania, or lose their irritability altogether, giving rise to a marked loss of mental power.

To minimise these dangerous complications and sequelæ, it will be necessary, in addition to following out the general rules that would suggest themselves to one in such cases, such as preventing chill, supplying a light and easily assimilated diet, attending to the emunctories, etc., to administer oxygen and perform artificial respiration until at least consciousness is restored. By these means we shall raise the tension of the oxygen in the alveoli, provide the tissues with a more than adequate supply of oxygen, and thus enable the exhausted cells to recover their normal equilibrium more rapidly. After consciousness has been regained, in addition to giving the ordinary tonics, iron, quinine, phosphorus, and strychnine, some of the gland extracts might be tried with advantage, such as cerebrin and pituitary gland extract.

III.—ALEXANDER SCOTT, M.D., Assistant Physician, Glasgow Royal Infirmary.

Poisoning by Carbon Monoxide.

My experience and observations on poisoning by CO have been chiefly clinical, inasmuch as I have been able to study its effects and processes only when inhaled in quantity sufficient to cause poisonous symptoms, but insufficient to bring about actual death. The pure gas is rarely generated out of the chemical laboratory, and my knowledge of its deadly effects has been obtained from the "clear gas" of the ammonia works, the analysis of which is essentially uniform. It consists of—

⁴ Foster, *Textbook of Physiology*, 5th Edition, p. 154.
⁵ *Lancet*, vol. i, January 25th, 1896.

⁶ Brunton, *Pharmacology, Therapeutics, and Materia Medica*, 2nd Edition.
⁷ *Journal of Physiology*, vol. xviii, p. 506.

						per cent.
CO ₂	6.55
CO	25.57
H	4.80
CH ₄	5.57
O	0.52
N	56.99
						100.00

It will be quite unnecessary to discuss at length the properties of the various constituents of this gas, for if we exclude N, H, and CH₄, which in the circumstances are perfectly harmless, there remain only CO₂ and CO to be reckoned with. But while H, N, CH₄, and CO₂ are not severely poisonous, it is quite evident that their presence serves to intensify the action and modify the effect of the poison, inasmuch as they take the place of air, which when mixed with CO renders it less hurtful. It must be noted, however, that CO₂ is not a negative asphyxiant like H and N, but acts like a narcotic on the nerve centres. Here, however, it may be removed from further inquiry, for while 6.55 per cent. might be unpleasant or even injurious to health, although this quantity could never produce actual poisonous symptoms, it acts as a powerful adjuvant to CO. It has a specific gravity of 1.524, and being heavier mixes slowly with the atmospheric air. CO has a specific gravity of 0.968, and burns with a pale-blue flame producing CO₂. The combination of these two gases is most deadly—so small a quantity as $\frac{1}{2}$ per cent. of CO when mixed with CO₂ has proved fatal, more or less speedily, to human life—and if a sparrow happen to breathe this "clear gas" it drops down dead instantaneously.

This question of the deadly nature of the combination of CO₂ and CO was painfully demonstrated in what is known as the Crarae gunpowder explosion, which took place in September, 1886, and by which seven of the visitors lost their lives and forty others were rendered more or less unconscious. The composition was:

		per cent.	lbs.
CO ₂	...	27.5	3,575
CO	...	3.6	468
H ₂ S	...	1.0	130
N	...	11.2	1,456
H	...	0.1	13
CH ₄	...	0.1	13

In this accident immense volumes of the gas were evolved, and owing to its confinement, and to the high specific gravity of CO₂, it moved slowly onwards, and in the absence of wind rose but gradually by diffusion. This explains how it was that the first group of holiday people passed unscathed beyond the openings to the quarry from which the gas issued, whilst those who followed came in for the full effect of the poison of CO greatly intensified by its combination with CO₂. It is interesting to note that the analysis of this gas is very similar to that from the ammonia works, and as it has a somewhat pleasant odour, scarcely appreciable, the victims are enshrouded in the mists of death before they can be aware of their perilous position.

Of the three cases that have come under my observation the first was the most violent, the patient having inhaled this gas from the flues in a circumscribed area for about ten minutes. The second was overcome by the gas in an exhauster, out of which (it was thought) all trace of it had been removed; while the third, when engaged cleaning a tube in the open air, fell and remained unconscious for one hour. In the first case the face was ghastly pale, while in the other two cases there was the well-known florid tint. The absence of the redness in the first case appeared to be due to feeble cardiac action. It is said that the red tint is due to a chemical compound formed by the union of CO and the colouring matter of the blood, and that its absence may be caused by the presence of a large quantity of CO₂.

The pupils were dilated, the pulse full but remarkably slow, in the severe case only reaching 40 per minute. They all complained of singing in the ears, headache, giddiness, muscular relaxation, unconsciousness, followed in the acute cases by convulsions, tetanic spasms and dementia.

They were all healthy men with no neurotic tendency. Regarding their present condition I have to state that the patient who was only slightly affected made a good recovery without any nervous symptoms supervening. The young man, aged 24, who was poisoned in an exhauster is greatly

improved in intelligence, but after a lapse of 2½ years his memory is still very defective. The patient, aged 42, who suffered most severely from the poison has been an inmate of an asylum for the last twelve months and the superintendent writes to me that though his general health is much improved there is no change in his mental condition and that he considers the case to be one of confirmed dementia.

The morbid condition which gives rise to these symptoms are caused by the action of CO on the blood and by its toxic effect on the nervous system. It enters the blood through the lungs and forms carboxyhaemoglobin the presence of which is capable of being demonstrated both spectroscopically and chemically. Dr. Thorpe proved that 1 gr. of haemoglobin will take up 1.88 cc. of CO and from experiments made by Dresser upon animals, death was found to follow when the oxygen was reduced to 30 per cent. The chief characteristic of this carboxyhaemoglobin is its stability, for as yet no active and direct solvent has been discovered. In this respect it closely resembles methaemoglobin but it differs from it in this way that methaemoglobin is altered during asphyxia. Reducing substances are constantly present in the blood and it is a well-known fact that these even accumulate during asphyxia, but such agents have no effect on carboxyhaemoglobin which consequently cannot be removed during artificial respiration.

How is this stable compound eliminated from the blood when its presence is insufficient to cause death? Claude Bernard taught that blood charged with CO was absolutely unalterable, but this opinion was opposed by Schutzenberger, who proved that well-oxygenated blood lost from 3 to 4 cc. of its oxygen in an hour, and further experiments led him to the conclusion that in blood partially and fully charged with CO the loss per hour was seven or eight times less. M. de Saint Martin has recorded some interesting experiments which demonstrated clearly the fact—which was constant—that in a mixture of blood partly oxygenated and partly charged with CO, preserved from contact with the air at a temperature of 38° C.—a certain quantity of the CO disappeared—a result which he thought was due to the conversion of CO into CO₂.

Evidence of the toxic effect of the gas upon the nervous system is generally present but the cause of this is difficult to understand. When an animal is confined in a close chamber without oxygen it dies of convulsions, and Lauder Brunton in his paper "On the Nature of Inhibition and the Action of Drugs upon it," explains this on the hypothesis of interference by supposing that the absence of oxygen retards the transmission of impulses in the nerve centres; so that we get those which ought ordinarily to inhibit one another coinciding and causing convulsions. Now when we remember that, by the presence of CO, the oxygen-carrying power of the blood corpuscles is as Bernard expressed it, paralysed, it may be safely assumed that the tetanic spasms and convulsions may be wholly due to the absence of oxygen.

Certain workmen show a marked susceptibility to this form of poison, while others may be employed in the same way for years and hardly ever be affected. In this connection I have observed an interesting coincidence. Those men who are easily affected by alcohol are remarkably susceptible to the poison of carbon monoxide and *vice versa*. This is all the more remarkable when we consider that after absorption into the blood alcohol appears to form a compound with haemoglobin which takes up and gives off O less readily than haemoglobin itself. It might therefore be fairly concluded that the effect of the gas is entirely dependent on the quantity of oxygen in the blood.

In conclusion, allow me one word on treatment. What we have to combat are the asphyxia, the want of oxygen, and the presence of this stable compound carboxyhaemoglobin. To relieve the asphyxia carbonate of ammonia by inhalation, ether by subcutaneous injection and the administration of nitro-glycerine are indicated. With regard to the latter drug I would suggest that a single drop held in an easily dissolved tablet might be left in the hands of an intelligent workman ready for administration in emergencies.

The absence of oxygen may be replaced by the inhalation of that gas and the carboxyhaemoglobin can only be successfully treated by venesection and the transfusion of arterialised defibrinated blood.

IV.—STEWART LOCKIE, M.D.,
Senior Physician to the Cumberland Infirmary.
A CASE OF COAL GAS POISONING.

I OWE it to the fact that several years ago a case of fatal coal gas poisoning came under my observation that I have been asked to take part in the discussion. The case was that of a young man, assistant "boots" at an hotel, who retired to rest about half-past twelve at night in a small room without a fireplace and was discovered at 8.20 the following morning. When his fellow servant entered the apartment there was an overpowering smell of gas in the room, the sliding gaseliers were drawn down to its full extent, and one of the two jets was burning with the cock turned full. The "boots" tried to arouse his assistant, but failed to do so. Half an hour later I saw him. He was lying on the right side in the semiprone position. There was a little staining of the pillow near the position of the mouth by a brownish coloured fluid. Coma was profound, the face was livid, pupils were equal, neither abnormally contracted nor dilated, and sensible to light. Respiration was extremely irregular. After removing the patient to a larger apartment and establishing a current of fresh air through it, it was further observed that the pulse was feeble and excessively frequent (150) and that the axillary temperature was 102.8. The breath smelt of coal gas. The eyeballs were observed to roll about in a peculiar fashion. They were turned slowly to the extreme left, as if the patient were looking to the left, they then slowly returned to the median line, then back to the left and so on. The motion was almost rhythmical and nearly constant. A similar rotation of the eyeballs was observed by Dr. William Taylor in a case published by him in the *Edinburgh Medical Journal* for July, 1874.

The patient lived sixty-eight hours after he was found. It is unnecessary, nor would time allow of it, to dwell upon the details of his condition during that time. The principal points are the complete coma, the odour of the breath, the peculiar movement of the eyeballs, the high temperature (it reached at one time 106.2° in the rectum), and the corresponding frequency of pulse and respiration. At the necropsy, thirty-five hours after death, the vessels of the surface of the brain were observed much more full of blood than usual; the surfaces of sections of the brain were darker in colour than normal, the puncta cruenta more numerous, and studded all over the surfaces were small clots of extravasated blood; these were not observed in the cerebellum or medulla. The spinal cord was normal. The laryngeal surface of the epiglottis was mottled with pink spots, the lining membrane of the bronchial tubes was of a dark purple hue; the surfaces and sections of the lungs were of a dark claret colour, mottled with spots of a bright pink hue; a few bright pink spots were seen also on section of the left kidney.

As regards the general subject of coal gas poisoning, it seems desirable to touch on a few points. First, it has been repeatedly observed, and the case I have narrated is an example of it, that a proportion of gas in the air less than that required to form an explosive mixture is nevertheless sufficient to cause death when inhaled. According to M. Tourdes (quoted by Dr. Taylor) it requires a minimum of one part of gas to eleven of air to form an explosive mixture; whilst in his experiments on animals he found that an atmosphere containing $\frac{1}{15}$ th of gas caused the death of rabbits in nine, twelve, or fourteen minutes, and of pigeons in five minutes; that it proved fatal, though in much longer time, when it formed $\frac{1}{10}$ th of the atmosphere, and that forming $\frac{1}{10}$ th it still ultimately caused death. Secondly, it is well known that cases of coal gas poisoning have occurred when there is no appreciable odour of gas on account of it having passed through soil not yet saturated with the gas. By leakage from a main outside poisoning occurs sometimes in houses where gas is not even laid on.

I am indebted to the JOURNAL of our Association for a knowledge of Pettenkofer's observations on this subject.

It is an interesting question what are the effects on the human system of a contamination of the respired air by gas in smaller proportions than that required to produce symptoms of acute poisoning. Various effects have been attributed to it. In 1887¹ Dr. Corfield read a paper at one of the societies

on "Outbreaks of Sore Throats Caused by Slight Escapes of Gas," and narrated instances where small epidemics seemed to be caused by defective gas fittings, and ceased on the defects being remedied. I am not aware whether the occurrence of such an effect as this has been confirmed by other observers.

Nausea, giddiness, coldness of the body, and inaptitude for work were observed by Sir Benjamin Ward Richardson in his own person as the result of the contamination of the air of his library by the escape of small quantities of coal gas from faulty pipes. The symptoms led him at first to suspect stomach derangement, but noting the similarity of the symptoms to those he had experienced while experimenting with carbonic oxide, he was led at last to the real source of the mischief. A similar case is recorded by Dr. Ellis of the Royal Navy,² in which the symptoms were directly associated to the use of an india-rubber gas tube in the apartment and ceased on the discontinuance of the apparatus.

A remarkable case is recorded by Pettenkofer.³ It was that of a priest, who for several days had been extremely unwell without any appreciable cause. He had observed that he felt worse on very cold days. Typhoid fever was diagnosed, and one night it was expected he would die. One of the rev. gentleman's parishioners seeing him in this condition, declared her belief that he was suffering from gas poisoning, notwithstanding the fact that gas was not laid on in the house. She was, however, firm in her opinion, and although the medical attendant said that the patient was too weak to be moved she ordered a carriage, had him carried into it, and driven away to another house. By the time they had arrived at their destination, which was at no great distance, the rev. gentleman had so far recovered as to be able to step out of the carriage unassisted and walk up the steps of the house. This gentleman resided in a house with a friend and was accustomed to keep his own room very warm, much more so than that of his companion was. When the patient departed his room was ventilated and the fire allowed to go out. Next morning the occupant of the adjoining room awoke with precisely similar symptoms to those of his friend. A strict inquiry was instituted, and it was found that a leak existed in the gas pipe in the street. The gas had been drawn into the relatively warmer room in each instance.

V.—J. LORRAIN SMITH, M.D.,

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MR. LORRAIN SMITH observed that Dr. Haldane's observation that carboxyhaemoglobin was not a stable compound, and that the gas gradually diffused from the blood when the patient affected was placed in pure air, or preferably in an atmosphere of oxygen, was very valuable. It was also of great importance practically to note the distinction drawn by Dr. Davison between immediate effects and subsequent effects. The subsequent effects included various changes which might be very severe. There also occurred a lowering of the resistance to microbes—for example, the pneumococcus.

VI.—T. W. PARRY, M.R.C.S., J.P.,
Glamorgan.

MR. PARRY asked Dr. Haldane if he had examined the blood of the man who was rescued alive after being exposed to carbon monoxide in a colliery accident for twelve hours, and if he could account for the recovery of this man while those around him died. He wished further to know if the gas referred to was before or after combustion.

DR. HALDANE'S REPLY.

DR. HALDANE, in his reply, said that Dr. Davison would, no doubt, be interested to learn that the percentage of carbon monoxide in the gas of Belfast varied between eighteen and twenty-two, owing to admixture with water gas by the corporation. In reference to treatment he called attention to the fact, particularly observed among the rescuers at Micklefield, that a partially poisoned patient when brought suddenly into cool air dropped down as if shot, and remained unconscious for some hours, but could be brought to by the admin-

¹ *Lancet*, vol. i, 1887, p. 828.

² *BRITISH MEDICAL JOURNAL*, vol. i, 1884, p. 824.
³ *Lancet*, vol. i, 1887, p. 965.

istration of oxygen. He thought, however that it was no good giving the gas later than an hour or so after exposure to carbon monoxide. In the case mentioned by Mr. Parry the patient, though almost dead when found, had no carbonic oxide in his blood twenty-four hours later; his recovery was probably due to the fact that he was working near the shaft at the time of the explosion, which occurred between the other victims and the shaft. Carbon monoxide was also absent from the blood in another case, in which its inhalation proved fatal in a few hours by deprivation of the tissues of oxygen.

THE LIMITATIONS TO THE ANTIDOTAL POWER OF ANTITOXINS,

AS ILLUSTRATED IN THE ANTAGONISM BETWEEN ANTIVENENE AND SNAKE VENOM; AND THE ORIGIN OF THE ANTIDOTAL CONSTITUENT OR CONSTITUENTS OF ANTIVENENE.

By T. R. FRASER, M.D. F.R.S.,

Professor of Materia Medica and Clinical Medicine, University of Edinburgh.
WHEN invited to make a communication to this Section on the subject of the serum treatment of snake poisoning I felt some doubt as to the branch of the subject I could select with best advantage, for I have only recently made several communications in which the more important of the results of my experimental work have been published.

It may not be superfluous again to draw attention to the circumstance that some knowledge of an effective means for producing protection against serpents' venom has probably been in existence from a remote period of time, and has long been, and is now being, practically applied by uncultured tribes and nations. The work of all modern investigators, begun by Sewell, Kauffmann, and Kanthack, and continued by Phisalix and Bertrand, and—with even more valuable and definite results—by Calmette, may thus in a sense be regarded as a continuation of the crude experiments of our ancestors, and a reproduction of some of the therapeutic facts which they had already discovered.

The boundaries of the subject have however, been widely extended. Restricting attention to these branches of it which I have myself experimentally examined, it has now been shown that the administration by subcutaneous injection of gradually-increasing doses of venom can produce so remarkable a protection that an animal may become able to receive in one single subcutaneous administration, and without obvious injury, a dose of cobra venom sufficient to kill fifty animals of the same species and weight (Fig. 1); that the blood

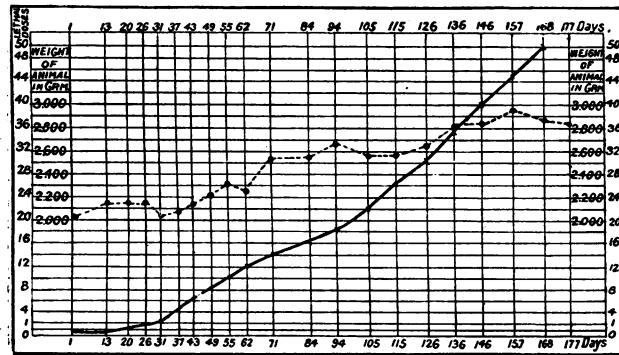


Fig. 1.—Immunisation of a rabbit against 50 times the minimum lethal dose of cobra venom. The crosses connected by the continuous line represent administrations of venom. The dots connected by the interrupted line represents the weight of the animal.

serum of animals thus artificially protected possesses powerfully antidotal qualities, while these qualities—although in a much smaller degree—are also possessed by the blood serum of venomous serpents themselves: that the antidotal qualities of the blood serum of artificially-protected animals are exhibited not only against the venom by which protection has been produced, but also—although to a relatively feeble degree—against the venom of other species of serpents; that this antivenomous serum, or antivenene, is able to prevent death

from otherwise lethal doses of venom, not only when it is subcutaneously injected but also when it is introduced into the stomach; and, further, that *venom* itself, when introduced into the stomach, is able to prevent death from being produced by the subcutaneous injection of doses of venom that would otherwise have proved fatal.

In this general statement of results several practically important and widely interesting questions are suggested which invite discussion. I propose to consider as briefly as possible two of these questions.

The Limitations to the Antidotal Power of Antitoxins.—When endeavouring to define the antidotal value of the blood serum of animals protected against serpents' venom, facts were ascertained which appeared to show that too little attention may have been given to the limitations of this antidotal power when estimating the therapeutic value not only of antivenene, but also of antitoxins of disease. This estimation is frequently based upon the dose of antitoxin required to prevent death from about, or a little more than, the minimum lethal dose of the toxin when the two substances are mixed together before being administered. As this basis gives much more favourable results than any other that could be adopted, while it alone affords no indication of the much larger quantity of antitoxin required to prevent death when administered after the toxin, it is obvious that an exaggerated conception is likely to be formed of the therapeutic value of the antitoxin.

It is of course apparent that in any given condition of administration the effective dose of the antitoxin must bear a certain relation to the dose of the toxin to be antagonised, but it may not be realised, and experiments on pharmacological as distinguished from chemical antagonism do not suggest how great are the differences when the conditions of administration are changed. For example, when serpents' venom and antivenene are mixed together *in vitro*, and thereafter injected under the skin of a rabbit, slightly more than the minimum lethal dose of venom may be prevented from producing death by 0.0004 c.cm. of antivenene per kilo. of animal, one and a-half the minimum lethal dose of venom by 0.25 c.cm. of antivenene per kilo., twice the minimum lethal dose of venom by 0.35 c.cm. of antivenene per kilo., thrice the minimum lethal dose by 0.65 c.cm. of antivenene per kilo., four times the minimum lethal dose by 1.2 c.cm. of antivenene per kilo., five times the minimum lethal dose by 1.5 c.cm. of antivenene per kilo., eight times the minimum lethal dose by 2.5 c.cm. of antivenene per kilo., and ten times the minimum lethal dose by 3.4 c.cm. of antivenene per kilo. (Fig. 2).

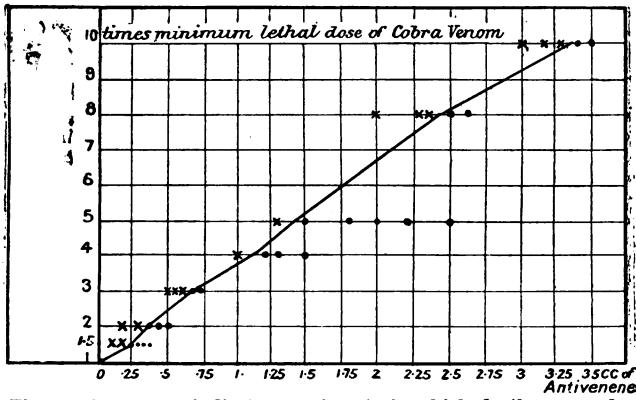


Fig. 2.—The crosses indicate experiments in which death occurred, the dots those in which recovery occurred.

Considering that slight experimental errors are unavoidable in such experiments, these results show an almost precise and directly proportional relationship between the dose of venom and the dose of antivenene required to antagonise it. They, however, give but little indication of the dose of antivenene required to prevent death in other conditions of administration. If, for instance, the two substances be still simultaneously injected, but without previous admixture, and the one into a different subcutaneous region from the other, 3.5 c.cm. of antivenene per kilo. is required to prevent death from one and a-half the minimum lethal dose of venom; and

with this dose of venom almost the same dose of antivenene is necessary when the venom is injected thirty minutes before the antivenene, thus reproducing the conditions of therapeutic administration. The contrast between the results of experiments *in vitro* and of such experiments as the last is even more conspicuously displayed when the minimum lethal dose of venom, or a little more than this dose, is adopted as the basis of comparison. If the antivenene be subcutaneously injected half an hour after the injection of this dose of venom, it is found that the smallest dose of antivenene that can prevent death is 0.65 c.cm. per kilo. of animal, or a dose which for the same dose of venom is so much as 1,600 times larger than is required when the two substances are mixed together before administration.

If the therapeutical value of an antitoxin be estimated by determining its antidotal power when mixed *in vitro* with its toxin, it is apparent that exaggerated and fallacious conceptions may be formed of the antidotal value of the antitoxin. So important a fact, for example, is likely to be overlooked as that, with even the most powerful antivenomous serum which has yet been prepared, so large a quantity as from 10 to 11 ounces (about 300 c.cm.) injected subcutaneously, is probably necessary for the purpose of preventing death in man after a minimum lethal, or little more than a minimum lethal dose of cobra venom has been received.

The Origin of the Antidotal Constituent or Constituents of Antivenene.—It is impossible to consider the great difference between the dose of antivenene required when the two substances, though in each case simultaneously administered, are, in the one case, mixed together before injection, and, in the other, not so mixed, without having the suggestion originated that the antidotism is not the result of any physiological action, but rather of a chemical reaction between antivenene and venom. This suggestion receives further support from the circumstance, observed in several experiments, that the antidotal efficacy of the antivenene may be increased by lengthening the period of time during which the two substances are allowed to remain in contact after they had been mixed together. For example, while 1.3 c.cm. of antivenene per kilo., mixed *in vitro* with five times the minimum lethal dose of venom, was followed by death when the two substances had been left together for five or for ten minutes, this mixture, on the other hand, was followed by recovery when the interval before administration was extended to twenty minutes or longer.

These and other facts, which I have elsewhere described, appear to show that the administration of a succession of gradually increasing doses of venom causes an antidotal substance slowly to accumulate in the body until the quantity becomes sufficient to prevent otherwise lethal doses of venom from producing death, and, it may be, from even producing any symptoms of poisoning. This substance is found in the blood serum, which may be dried without any loss of its original antidotal power, and may even be allowed to undergo a certain amount of putrefactive change, with microbial proliferation, not only without depreciation, but with a measurable increase in its antidotal value.

In order to account for the presence of this substance in the body, several theories might be advanced, including those which have attached themselves to the general subject of serum therapeutics.

A number of experiments which I have made, in some of which antivenene and in others venom itself was introduced into the stomach, appear to throw some light upon this subject. The experiments with antivenene were undertaken, in the first place, with the object of determining if by the stomach administration of a succession of doses an animal would finally become so far protected as to be able to resist a lethal dose of venom. It was found that protection could thus be produced. On afterwards varying the experiments so as to test the protective influence of a single dose of antivenene, it was also found that protection against a lethal dose of venom, administered subcutaneously, could be equally well produced by a single dose of antivenene introduced into the stomach, and that this protection could be accomplished in so short a time as two hours.

Having thus determined that the stomach administration of antivenene, as well as its subcutaneous administration, confers protection against lethal doses of serpents' venom, ex-

periments were made to ascertain if the stomach administration of venom itself is also capable of doing so. Cobra venom was introduced in a series of gradually increasing doses into the stomach of a cat, until finally, at the end of four months, it received a single dose estimated to be at least eighty times the minimum lethal if subcutaneously injected; and although no general poisonous symptoms had been produced, it was found that the cat had become so far protected that it could now receive by subcutaneous injection one and a-half the minimum lethal dose of cobra venom, without any other injury than some irritation at the seat of injection. This experiment was repeated in its chief details on several white rats, and the results were the same.

Another series of experiments was undertaken for the purpose of ascertaining if protection could also be produced by a single dose of venom introduced into the stomach. Into the stomach of each of several white rats a single dose was introduced, equivalent, if subcutaneously injected, to 10, 50, 200, 500, and 1,000 the minimum lethal. Even the largest of these doses produced no obvious symptom of poisoning, excepting some evidence of gastro-intestinal irritation. Nevertheless, so perfect protection was produced that the subsequent administration by subcutaneous injection, of a little more than the minimum lethal dose of venom now failed to produce death, provided certain time limitations were attended to between the two administrations. These time limitations, however, are also of interest, for they indicated that with the largest of the above doses protection may continue for so long as five or six days, and that with nearly all of these doses the protection is so rapidly produced that it may be accomplished within two hours after the venom has been introduced into the stomach.

The significant, and in many respects, unexpected result has thus been obtained that serpents' venom introduced by a single administration into the stomach, in large and sometimes enormous quantity—(in a quantity, for instance, which if injected under the skin is sufficient to kill 1,000 animals of the same species and weight, or if only the $\frac{1}{100}$ th part of the quantity administered had been absorbed from the stomach into the blood would have produced not merely severe toxic symptoms, but actually death)—while it failed to produce any symptom indicating the absorption into the blood of any poisonous substance, nevertheless produced protection sufficient to prevent death from the subcutaneous injection of more than a lethal dose of venom. There is a probable significance, further, in the general resemblance between the results of these experiments and of those already alluded to in which antivenene, and not venom, was introduced into the stomach. It is, indeed, difficult to account for them otherwise than by supposing that the venom, while in the stomach, had been subjected to a process of analysis, by which constituents which are poisonous had failed to be absorbed into the blood, or had been destroyed in the stomach or upper part of the alimentary canal, while constituents which are antivenomous, or rather antidotal, had passed into the blood in sufficient quantity to protect the animals against otherwise lethal administrations of venom.

The facts that have been stated appear to show that the antidotism produced by antivenene cannot be explained by phagocytosis. This process could not, of course, operate *in vitro* in solutions which are free from organised structures; and when solutions of antivenene and venom, mixed together *in vitro*, are afterwards injected under the skin, it is inconceivable that an increase in the quantity of antivenene amounting to only the $\frac{1}{100}$ th part of a c.cm. could cause such an increased proliferation of leucocytes as to prevent a lethal dose of venom from producing death, whereas a dose of antivenene only the $\frac{1}{10}$ th part of a c.cm. smaller is unable to do so.

The explanation which attributes successful antidotism to a power, supposed to be possessed by antivenene or venom, of increasing the resistance of tissues, seems equally untenable. In so far as antivenene is concerned, it is opposed, for instance, to the facts that so great a quantity of it as 0.42 c.cm., or nearly half a c.cm. per kilo., is required to prevent death when given thirty minutes before a lethal dose of venom; whereas, for the same dose of venom, only 0.0004 c.cm., or the $\frac{1}{1000}$ th part of a c.cm., or nearly the $\frac{1}{100}$ th part of the former dose, is sufficient when it is mixed with the venom before adminis-

tration, and in circumstances, therefore, which are much less favourable for the production by the antivenene of this supposed increase in the resistance of the tissues. In so far as venom is concerned, this explanation, however plausible it may appear when applied to the production of protection by the administration over periods of several weeks of a succession of gradually increasing doses of venom, is irreconcilable with some of the facts observed in the production of protection by the stomach administration of venom, and especially that within less than two hours after this administration, and although absolutely no disturbance of the normal physiological condition of the animal can be observed, so complete protection or immunisation may be effected that more than a lethal subcutaneous dose of venom is now unable to produce death. All the facts, however, are reconcilable with the suppositions that protection or immunity is chiefly due to the accumulation in the blood of an antitodal substance, and that this substance originates, at least in part, from the venom itself, and is normally one of the constituents of the venom.

Several months ago I had expressed a hope, or rather a conviction, that the latter suppositions, already strongly supported by the remarkable results obtained when venom is introduced into the stomach, would by-and-by receive further support from the results of analytical processes conducted outside of the living body.

In a paper published in the *Comptes Rendus* of June 15th, M. Phisalix, who, with M. Bertrand, has for several years been engaged in an investigation of the properties of the venom and blood of vipers, announces that when this venom is filtered through porcelain a filtrate is obtained possessing antitodal properties and almost destitute of toxic action.

If these results be confirmed, the explanations which I have advanced of the cause of protection and of the origin of the antitodal constituent or constituents of antivenene will be placed on a more secure basis. Already, however, the facts which have been established seem to require that the theories of immunisation as applied to the toxins of disease, and the considerations which regulate the therapeutical applications of antitoxins, should be reconsidered in many particulars.

Professor CALMETTE (Director of the Pasteur Institute in Lille), who spoke in French, said: I regret extremely Professor Fraser's absence, as I should have liked to have entered into a personal discussion with so very distinguished an experimenter on this question of venoms, to the study of which both of us have devoted so many years. Professor Fraser rightly insists in his paper on the necessity of measuring exactly the antitodal power of antivenomous serums. He proposes to take as the basis of this measurement the quantity of antitoxin necessary to destroy the effect of a dose of venom calculated as one and a half times that which would be fatal to an animal of a given weight; the antitoxin and the venom must not be mixed, but injected into different parts of the animal's body. I have myself put forward a method at a meeting at the Laboratories of the Royal Colleges in London, where I made a series of experiments last Monday (July 27th), which appears to me to be more exact and more easy to apply than that indicated by Professor Fraser. I consider that his method takes as the basis of estimation too small a quantity of venom, since one often finds very great differences between the sensibility of various animals to subcutaneous inoculation of venom. The method which I have suggested depends upon the following facts. One determines first with any particular venom the dose causing death in twenty minutes when injected intravenously. This having been ascertained, one takes as the basis for determining the antitoxic power of a serum the quantity of it necessary to immunise immediately 1 kilo. of the animal by intravenous injection; the serum is injected fifteen minutes before the venom. The exact power of any given serum can thus be determined in thirty-five minutes, and there is no chance of error, since the dose of serum worked with is at least ten times as great as the minimal mortal. One c.cm. of my serum per kilo. of bodyweight suffices to prevent death from the intravenous injection of venom, and we shall certainly soon succeed in obtaining a still more active product. The mean quantity of venom injected by a cobra at each bite is about 10 to 15 mg. (weight of venom in the dry state). Now 2 c.cm. of my serum are enough to prevent

death in a rabbit an hour and a-half after injection of a dose of venom equal to 5 mg., which would ordinarily be fatal in two or three hours. I reckon, therefore—and this is borne out by the experiences in man which I have detailed—that 10 or at most 20 c.cm. of my serum would be amply sufficient in the treatment of a poisoned bite, instead of 200 or 300 c.cm. as recommended by Professor Fraser. The process of vaccinating animals by ingestion, described by Professor Fraser, is full of interest. I have not succeed in confirming it, probably because I have not operated under the same conditions as he. I have made guinea-pigs and fowls swallow large quantities of venom, and even of fresh poison glands, and have not found that their serum became antitoxic in consequence. These animals have, on the other hand, succumbed to the subcutaneous injection of twice the mortal dose of venom. From the practical point of view this process of immunisation by ingestion would require too much venom to be of use in animals destined for the production of serum. As regards Professor Fraser's views on the subject of immunity produced by venom, I do not think with him that there is produced in the blood of the animals a chemical substance derived from the venom, and for the following reason. A test tube mixture of a powerful dose of venom—say ten times the mortal—with a sufficient quantity of antitoxic serum, 1 c.cm. of my actual serum injected under the skin of a rabbit is harmless. If the mixture is heated to 80° for five minutes in a sealed tube and then injected under the skin of a rabbit, it is just as fatal as if no antitoxic serum had been added. The reason of this is that by heating to 80° the serum has lost its antitoxic power, while the venom is unaffected and recovers its full toxicity. The venom then is not altered by being mixed with serum, but the simultaneous injection of antitoxin prevents it from acting on the cells of the organism. I demonstrated an experiment in London which shows in quite a different manner that immunity is conferred by the serum instantaneously without any time being left for the cells to secrete a chemical antitoxin. I injected 3 c.cm. of serum into the vein of the ear of a rabbit; a quarter of an hour later I injected into the vein of the other ear 2 mg. of venom, a dose which killed the control animal in twenty minutes. The experimental rabbit was unaffected. The immunisation conferred by the serum is then almost instantaneous, and I do not see how immunity thus produced can be explained otherwise than as a sort of immediate insusceptibility of the cells in respect to the venom.

ANTIDIPHTHERITIC SERUM AND ITS PREPARATION.

By T. J. BOKENHAM, M.R.C.S., L.R.C.P.,
Late Research Scholar, British Medical Association.

The subject of serotherapeutics has already been dealt with in such detail in the medical journals that some excuse is perhaps needed to justify one in bringing it before the Section of Pathology at this meeting of the Association. The journals have of course been full of the results obtained by serotherapy in the treatment of diphtheria, and they have also from time to time contained accounts, more or less detailed, of the mode of preparation, testing, and issuing the serum for use from the various laboratories in England and abroad. During the past two years, however, I have given a great part of my time to the preparation of antidiphtheritic serum, and to studying the most suitable means for securing its uniform activity. During that time I have received very numerous letters from practitioners asking for all sorts of details as to the method of preparation; how uniform potency is secured; how the tests are carried out in my own laboratories; and how the serum should be used in actual practice. These showed me that something was needed in addition to the descriptions which had appeared from time to time; and I thought the present meeting afforded a very excellent opportunity for giving as briefly as possible a practical demonstration of the whole of the processes employed in preparing antidiphtheritic serum, commencing from the selection of the diphtheria bacillus destined to produce the toxin needed for immunisation, and finishing with a description of the technique of the method by which the serum is put into bottles for use.

THE DIPHTHERIA BACILLUS TO BE SELECTED.

Roux and Behring found that the best method of preparing a strong toxin was to cultivate the bacillus in a free current of oxygen, and Roux finally employed, and employs still, very wide flat flasks through which a current of air can be continuously drawn by means of a suction pump. These flasks are capable of holding a large quantity of bouillon in a layer of small depth. Roux inoculates these flasks, and allows the bacilli to grow at a temperature of 37° C. for three weeks or a month, possibly longer, with a constant current of air passing over the surface. The method of Roux has been very widely adopted, and is still employed in most laboratories. In the course of last year, however, I paid a visit to the Institut Séro-Thérapeutique at Brussels, and studied the methods employed by my friend, Dr. Funk, the Director of that Institute. His results convinced me that it was by no means necessary to employ the complicated method of aération devised by Roux, and that by using a very virulent bacillus a toxin could be obtained quite strong enough for ordinary purposes—indeed, many times stronger than the Behring “normal toxin.” Since that time I have, therefore, abandoned the method of Roux, and adopted one similar to that which I saw in action at Brussels.

It is a matter of great importance to observe the mode of growth of the bacillus itself. In order to obtain an active toxin, it is desirable that the bacillary growth should take place chiefly in the form of a dense white pellicle on the surface of the bouillon. The bacilli, as they multiply, are then brought into contact with a free supply of oxygen, and form their toxic products under the best possible conditions. It is also most important to keep the flask undisturbed from the moment that the pellicle has commenced to form, in order to avoid breaking up the film of bacilli. After about a fortnight or three weeks of incubation at 37° , the culture may be filtered through a sterile porcelain filter, and if the process has been carried out with proper care and a sufficiently virulent bacillus employed, it will be found that the toxin yielded is of such a strength that a dose of from 1 to 5 cgs. is fatal within forty-eight hours to small guinea-pigs. It is the experience both of Dr. Funk and myself that unless a good firm pellicle is formed the resulting toxin is seldom satisfactory in power.

Before using such a toxin for immunising horses one should first determine its activity. This is ascertained by tests carried out on small guinea pigs. We have not been satisfied with any toxin for immunising purposes, unless the lethal dose is at the most 5 cg., such a dose producing death in 300 g. guinea-pig within about forty-eight hours. Such a toxin I have employed constantly for nearly twelve months, and it will be observed that it is a good deal more powerful than the toxin adopted by Behring as a standard.

In using such a powerful poison the selection of the breed of horses to be subjected to the immunising process is of great importance. That was brought to my notice by a perusal of the admirable results obtained in Italy last year. Some samples of antitoxin which I obtained from Italy were far more active than any obtainable elsewhere. I sought for some explanation of it, and I believe was successful in finding one. In Italy the animals used in preparing serum were, I understand, thoroughbred horses obtained from racing stables. Such animals seemed to stand the injection of toxin extremely well; they showed very slight reaction, either local or general. The process of immunisation was extremely rapid, and the condition of immunity when once established could be maintained with a minimum of trouble. The risk of losing animals as the result of an over-dose of poison seemed also to have been reduced to a minimum.

Since making that discovery I have always endeavoured to select horses which are as well bred as possible, and have gradually succeeded in weeding out from the stables several of the old horses which they first used, and replacing them by thoroughbreds. It is quite a mistake to suppose, as has been frequently stated by writers in the medical journals, that any old horse is good enough for the production of antitoxin. With old horses the process of immunisation is unnecessarily long, and the risk of losing them during that process is enormous.

THE PROCESS OF IMMUNISATION.

For the first few injections it is necessary to use extremely

small and carefully measured doses of toxin. Roux recommended that the toxin used for the first few injections should be mixed with some mitigating substance, such as iodine trichloride or Gram's fluid. Such a mixture may be necessary in low-bred animals, but it is not so necessary in the case of thoroughbreds. I have found that a thoroughbred horse can almost invariably resist without undue disturbance a dose of 0.25 c.cm. of a toxin which is fatal to guinea-pigs in the dose of 4 or 5 cg.

The process of immunisation, as is well known, consists in the continuous administration of graduated doses of toxin until the animal treated shows neither serious local nor general disturbance as the result of the injections. The initial injections, being small in bulk, may be conveniently made under the skin of the shoulder, but when larger doses are required it is found more convenient to give the toxin by intravenous injection, and I have here a syringe which I find very convenient for the purpose. It consists of the ordinary serum syringe to which I have added a three-way stopcock. To the main nozzle is attached an injection needle by means of a rubber connection; to the side branch is attached another rubber tube, which is passed through a cotton wool plug into a bottle containing toxin. By this arrangement any amount of toxin may be injected with a minimum amount of trouble and inconvenience both to the operator and the animal. I have found it extremely useful in practice.

At various stages of the immunisation it is desirable to test the antitoxic power possessed by the serum. For this purpose a little blood can be obtained from the jugular vein by means of a small aspirating syringe. The protective power of the serum obtained from this blood can be readily ascertained by test experiments on guinea-pigs. After three or four months, if the immunisation process has been carried on carefully and steadily, the serum should possess an antitoxic power of at least 500 to 700 units per 10 c.cm. By the employment of such powerful toxins as those which I have already described it is no longer necessary to wait from six to twelve months before being able to obtain a serum of sufficient strength for clinical use.

METHOD OF BLEEDING THE ANIMALS.

There are two methods by which the blood can be obtained in sufficient quantities for practical use. The first is that generally employed, and consists in the insertion of a large cannula into the jugular vein, which has been previously distended with blood by means of a cord passed round the base of the neck and pulled tight. To the end of the cannula is attached an indiarubber tube, which is placed in communication with the bottle destined to receive the blood. In this manner the blood can be obtained in an aseptic condition, provided the instruments and collecting flasks be sterilised previous to use. In some cases, however, when the animal has only a small or not readily accessible jugular vein it is somewhat difficult to insert the cannula, and the process occasionally also becomes tedious from coagulation of the blood taking place somewhere in the lumen of the tube. Another and somewhat more convenient method is one which I have myself adopted. No special care is necessary to secure complete asepsis, and the only instrument required is an ordinary sharp fleam, such as is employed by veterinary surgeons. With this instrument I make an incision in the course of the jugular vein and collect the stream of blood, which issues with some force from the wound, in flasks capable of holding about $1\frac{1}{2}$ litre. These flasks are of a form commonly known as filter flasks. When filled they are transferred to an ice-safe or cool chamber, where they are allowed to remain sheltered from light from twenty-four to thirty-six hours, in order to allow complete coagulation to take place. About 8 litres of horse's blood will, as a rule, yield at least $3\frac{1}{2}$ litres of clear serum.

The next point is to ascertain the antitoxic value of the serum. For this purpose one must take a series of guinea-pigs of fairly uniform weight. One of these is used as a control animal, and receives a dose of diphtheria poison corresponding to the lethal amount. The others receive mixtures of various proportions of the serum which is to be tested with ten times the lethal dose of diphtheria toxin. I have a series of slides which I will throw on the screen, and

which illustrate in tabular form, better than any words of my own could do, the details of the test above alluded to.

Dose of Serum.	Guinea pig Weight.	Reaction.	Died after	Living in	Dose of Toxin.	Date of Test.
$\frac{1}{10}$ c.c.m.	490 g.	Swelling	52 hours	—	0.2 g.	Jan. 30th, 1895.
$\frac{1}{10}$ c.c.m.	475 g.	?", "	56 hours	6 days	","	
$\frac{1}{10}$ c.c.m.	470 g.	" Nil	—	6 days	","	
$\frac{1}{10}$ c.c.m.	500 g.	" Nil	40 to 48 hours	—	","	
Control	495 g.	—				
$\frac{1}{10}$ c.c.m.	400 g.	Swelling	54 hours	—	0.2 g.	Feb. 11th, 1895.
$\frac{1}{10}$ c.c.m.	385 g.	?", "	55 hours	—	","	
$\frac{1}{10}$ c.c.m.	390 g.	" Nil	—	7 days	","	
$\frac{1}{10}$ c.c.m.	424 g.	" Nil	—	7 days	","	
Control	408 g.	—	50 hours	—	","	
$\frac{1}{10}$ c.c.m.	305 g.	Swelling	3 days	—	0.2 g.	Mar. 6th, 1895.
$\frac{1}{10}$ c.c.m.	295 g.	Slight ditto	—	6 days	","	
$\frac{1}{10}$ c.c.m.	310 g.	" Nil	—	6 days	","	
Control	328 g.	—	40 to 48 hours	—	","	
$\frac{1}{10}$ c.c.m.	305 g.	Swelling	4 days	—	0.3 g.	May 9th, 1895.
$\frac{1}{10}$ c.c.m.	290 g.	?", "	—	6 days	","	
$\frac{1}{10}$ c.c.m.	325 g.	" Nil	—	6 days	","	
Control	300 g.	—	48 hours	—	","	
$\frac{1}{10}$ c.c.m.	280 g.	Swelling	74 hours	—	0.25 g.	June 13th, 1895.
$\frac{1}{10}$ c.c.m.	300 g.	Slight ditto	—	6 days	","	
$\frac{1}{10}$ c.c.m.	293 g.	" Nil	—	6 days	","	
Control	305 g.	—	52 hours	—	","	
$\frac{1}{10}$ c.c.m.	285 g.	Swelling	7 days	—	0.1 g.	July 12th, 1895.
$\frac{1}{10}$ c.c.m.	270 g.	" Nil	—	7 days	","	
$\frac{1}{10}$ c.c.m.	290 g.	" Nil	—	7 days	","	
Control	257 g.	—	52 hours	—	","	
$\frac{1}{10}$ c.c.m.	233 g.	" Slight swelling	—	6 days	0.5 g.	Sept. 24th, 1895.
$\frac{1}{10}$ c.c.m.	250 g.	" Nil	—	6 days	","	
$\frac{1}{10}$ c.c.m.	251 g.	" Nil	—	6 days	","	
Control	262 g.	—	2 days	—	0.05 g.	
$\frac{1}{10}$ c.c.m.	303 g.	Swelling	7 days	—	1.0 g.	Dec. 5th, 1895.
$\frac{1}{10}$ c.c.m.	290 g.	Slight ditto	—	7 days	","	
$\frac{1}{10}$ c.c.m.	317 g.	" Nil	—	7 days	","	
Control	330 g.	—	2 days	—	0.1 g.	
$\frac{1}{10}$ c.c.m.	325 g.	Swelling	4 days	—	0.2 g.	May 5th, 1896.
$\frac{1}{10}$ c.c.m.	310 g.	?", "	—	6 days	","	
$\frac{1}{10}$ c.c.m.	290 g.	" Nil	—	6 days	","	
Control	360 g.	—	53 hours	—	0.02 g.	

It will be observed that they are taken from my notebook over a period of about eighteen months, and I would mention that they are typical of many dozens of similar investigations, all of which time does not allow me to bring before you. In examining the details of these charts, it will be observed that the doses administered are not uniform throughout. During the earlier periods a different standard of immunity value was adopted, and a serum was issued possessing such a strength that 1 g. would surely protect 50,000 g. of guinea pig against a lethal dose of diphtheria toxin. In the later records, which correspond roughly to the period during which the Behring standard was adopted, the serum was tested in regard to its power of protecting small guinea-pigs against ten times the lethal dose of toxin; thus, a bottle which contained 10 c.c.m. and was said to have an immunity value of 600 units contained a serum of which $\frac{1}{10}$ g. completely protected the animal against ten times the lethal dose of toxin.

The serum having been tested and found active, it has to be sterilised before it can be used with safety. For that purpose I have had a large pressure filter constructed, somewhat after the model originally designed by d'Arsonval, through which the serum can be forced by means of pressure supplied by

liquified carbonic acid gas, the pressure required being regulated by means of one of the very convenient pressure valves made for me by Messrs. Uhlmann and Keutgen, of Lime-street, London, E.C. I have the whole apparatus here before you, and, as I have already charged it with serum requiring filtration, I propose to demonstrate the process practically to you.

DEMONSTRATION.

It will be seen that the conditions under which the filtration takes place are such as to almost absolutely preclude the possibility of the serum which has been sterilised by passage through porcelain filter tubes becoming again contaminated by the introduction of chance microbes from the air. In order to carry out the test of the process, and to charge each bottle with the required quantity of serum, I employ

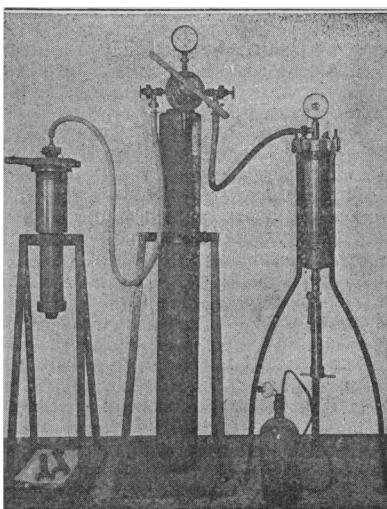


Fig. 1.—Apparatus used for filtering serum, showing two forms of pressure-filter, cylinder of CO₂, with regulating valve and receiver for filtered serum.

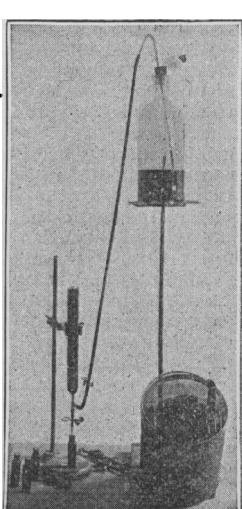


Fig. 2.—Apparatus used in decanting and measuring serum.

burettes of the model which I here show. By their use the measurements can be carried out with the greatest possible facility, and with practically no risk of contamination.

I may mention, finally, that no single bottle of serum is allowed to leave my laboratories for clinical use until it has been securely corked and sealed under my direct supervision.

THE EFFECTS OF INTERRUPTING AFFERENT AND EFFERENT TRACTS OF THE CEREBELLUM.

By J. S. RISIEN RUSSELL, M.D., M.R.C.P.,

Research Scholar to the British Medical Association; Assistant Physician to the Metropolitan Hospital; and Pathologist to the National Hospital for the Paralysed and Epileptic, Queen Square.

In one series of experiments the inferior peduncle of the cerebellum was divided on one side, and the results obtained in this way were controlled by experiments in which unilateral section of the lateral tracts of the medulla oblongata was performed, without injury to the pyramid or the posterior columns and their nuclei. Further control experiments consisted in dividing transversely the posterior columns and their nuclei a few millimetres above the calamus scriptorius on one side.

In another series of experiments the electrical excitability of the two cerebral hemispheres was tested and compared after section of one inferior peduncle of the cerebellum, and

after partial hemisection of the medulla, in which both pyramids were left intact.

A third series of experiments dealt with the ways in which convulsions induced by the intravenous injection of absinthe were modified by division of an inferior peduncle of the cerebellum, by partial hemisection of the medulla in which the pyramid was the only structure left intact, and by transverse section of the posterior columns and their nuclei, on one side, a few millimetres above the calamus scriptorius.

The most obvious results obtained in the first series of experiments consisted in rotation, disorders of motility, ocular displacements, muscular spasm, and blunting of sensibility. The direction of rotation was towards the side of the lesion, or, to take an example, in a left-sided lesion the animal rotated like a right-handed screw entering an object. The motor defects corresponded with those observed after ablation of one lateral half of the cerebellum, involving the two limbs on the side of the lesion and the opposite posterior limb. The eyes were displaced downward and to the opposite side from the lesion. Spasm in the back and neck muscles resulted in incurvation of the vertebral axis to the side of the lesion, and the general tendency was for the limbs on the side of the lesion to be flexed, while those on the opposite side were extended. The condition of the tendon reflexes was variable. The sensory defects corresponded closely in distribution to the motor, the limb in which the motor defect was most pronounced being that in which the sensory disorder was most marked.

While section of the lateral tracts of the medulla oblongata on one side gave results closely resembling those obtained after division of one inferior peduncle of the cerebellum, transverse section of the posterior columns and their nuclei on one side was responsible for very different results. All the phenomena met with after division of the inferior peduncle, or after section of the lateral tracts of the medulla, can be explained by supposing that they result from interruption of afferent impulses which reach the cerebellum under normal circumstances, with the exception of the spasm in the muscles, which is best explained by supposing that efferent impulses from the cerebellum, which normally control pontine or spinal centres, have been cut off.

The experiments in which the faradic excitability of the two cerebral hemispheres was compared, showed that the cortex of the hemisphere on the side opposite to that of the divided tracts was less excitable than was the cortex of the hemisphere on the same side. So that it seems as if the removal of some afferent inhibitory influence from one half of the cerebellum allowed this half of the organ to further inhibit the cortex of the opposite cerebral hemisphere.

This view is strengthened by the remarkable results obtained by the intravenous injection of absinthe in animals in whom one inferior cerebellar peduncle was divided, or in whom partial hemisection of the medulla was performed, for with the pyramidal system absolutely intact on both sides, there was an entire absence of contraction of the muscles of the anterior extremity on the side of the lesion, and diminution of contraction of the muscles of the posterior extremity on this side, as compared with the muscles of the opposite hind limb. Another possible explanation of these phenomena could be found by supposing that while some parts of the cerebellum are concerned in inhibiting the cerebral cortex, others are engaged in reinforcing pontine and spinal centres; but the results of unilateral ablation of the cerebellum make this explanation untenable. The results just described were only obtained when the convulsions were induced soon after the lesion, for when induced at some remote period, such as three weeks after the operation, the muscles of the anterior extremity on the side of the lesion contracted, though the contractions were much less powerful than were those of the opposite anterior extremity, and were often largely tonic in character.

Transverse section of the posterior columns and their nuclei alone on one side did not alter the character of the absinthe convulsions in such a remarkable manner as did division of the inferior peduncle of the cerebellum and partial hemisection of the medulla. After the lesion of the posterior columns the muscular contractions in the anterior extremity on the side of the lesion were less powerful than were those in the opposite anterior extremity, and there was more tonus and

less clonus than in the contractions on the opposite side. Both these characters were evident in the early convulsions of a series, but became much more pronounced in the later convulsions.

[The paper was illustrated by a lantern demonstration of tracings obtained of these muscular contractions resulting from excitation of the cerebral cortex with the induced current, and from the convulsions evoked by the intravenous injection of absinthe.]

SOME EFFECTS OF DIET ON THE EXCRETION OF URIC ACID.

By ALEXANDER HAIG, M.A., M.D.Oxon., F.R.C.P., Physician to the Metropolitan Hospital, and the Royal Hospital for Children and Women.

I HAVE for many years been pointing out that a large number of diseases are due, entirely due, to the presence of excess of uric acid in the blood and tissues. In the course of my investigations I discovered that uric acid could be introduced into the body and blood by the simple process of swallowing it. It had previously been believed and taught that uric acid when thus taken was converted into urea, and did not remain as uric acid in the blood or tissues. Now this discovery, made by me in 1892, has already given us a very great increase of power to control the quantity of uric acid in the body and blood, for it has shown that the uric acid of pathology is to a very large and important extent made up of the uric acid which is swallowed day by day in the food; and as it is quite easy to control this, we step at once into possession of a very important power of control over all diseases due to uric acid, in so far as they are functional and have not already produced structural and organic changes.

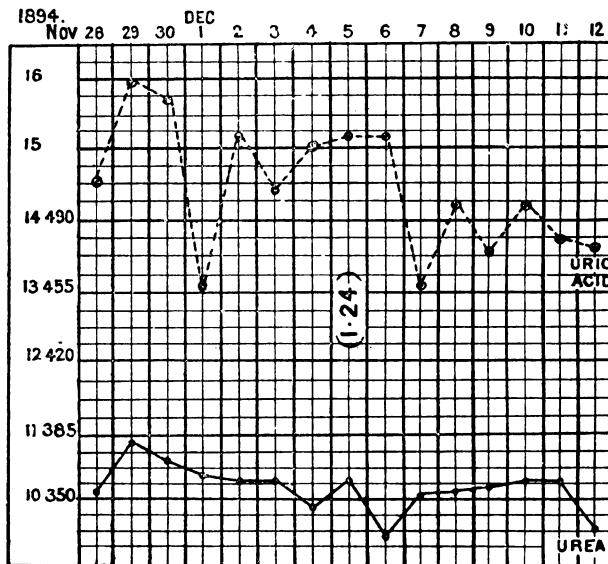


Fig. 1.—Fish and egg.

I propose now to show by means of curves some of the changes in the excretion of uric acid that can be produced by diet, and to mention shortly some of the diseases which are found to be more or less completely controlled by such diet.

Fig. 1 shows the excretion of uric acid and urea in a period in November and December, 1894, when animal food consisted of milk, cheese, fish, and eggs, and when tea and coffee were taken. We see here that uric acid is always considerably above urea, to which it bears a relation of about 1 to 24, and that from 3 to 5 gr. of uric acid passed through the blood every day.

Fig. 2 shows a similar curve in March, 1895, though here diet contained no tea or coffee and less animal food, but some little fish and egg were still being taken. Here also we see that uric acid is constantly above urea, bearing a relation to it of about 1 to 29, and that from 2 to 4 gr. of uric acid passed through the blood every day. With the condition of things represented in these figures, my notes show that the diseases due to uric acid—such as headache, mental depression, and the high blood pressure that goes with these—though far less marked and severe than on ordinary diet containing meat, soup and meat extracts were still far from being completely under control.

Fig. 3 shows the excretion in March, 1896, when milk and cheese were the only animal foods. Here uric acid is more below urea than above it, and bears the general relation to it of 1 to 36.

Fig. 4 is a similar curve from May, 1896, at which time the diet was just the same as at the time of Fig. 3. It is given to show that though excretion may fluctuate from day to day uric acid is never much more than 1 gr. above urea—that is to say, 1 gr. is the largest amount that ever passed through the blood in any one day. With this condition of things, the above-mentioned diseases are remarkable for their steady and complete absence.

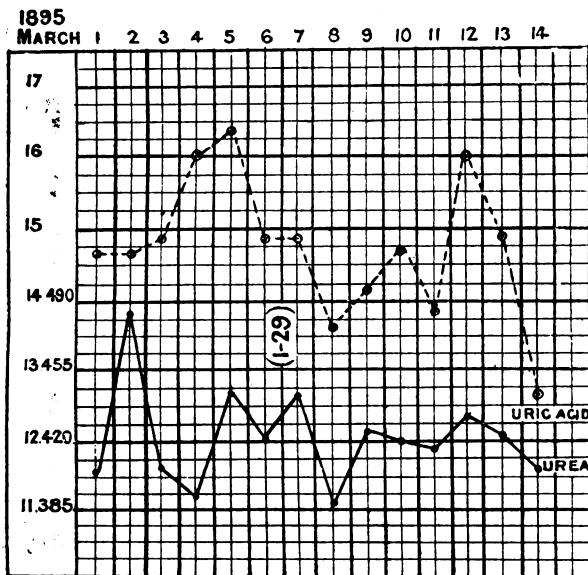


Fig. 2.—Fish and egg.

From these facts I think we may conclude that it is possible by avoiding entirely all animal foods that contain xanthine compounds or uric acid, and also tea, coffee, and cocoa—whose alkaloids are similar xanthine compounds—to limit very greatly the introduction of uric acid into the body, and when the stores and accumulations already in the body have been eliminated to keep the excretion of uric acid in the urine always below the relation to urea of 1 to 30, and that when this has been done all functional disease due to excess of uric acid in the body and blood will diminish and disappear.

Now it will very probably at once be asked how we are to tell in any given case when the body is clear of uric acid, and when the possessor of it may therefore expect freedom from uric acid disease? By altering the diet it is possible to diminish very decidedly the excretion of uric acid; and even in a few days to make it less than in Fig. 1, and perhaps even less than in Fig. 2; but it will take many months—possibly twelve to eighteen, or more—to clear out the stores and accumulations, and till this has been done uric acid will not stay permanently at the levels shown in Figs 3 and 4, and in a given case we may want to know how far elimination has gone.

Now Fig. 5 shows, I think, that this can be done by means of a dose of salicylate of sodium, for when the body is clear

of uric acid a dose of that drug will no longer make it rise to any great height above urea. This figure shows the excretion

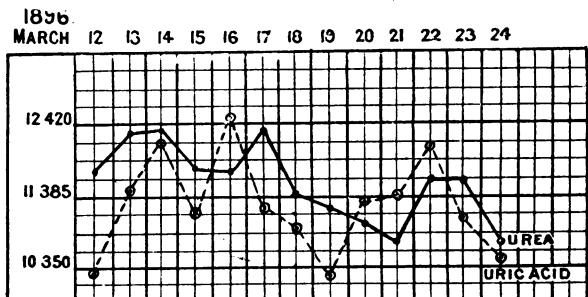


Fig. 3.—Milk and cheese.

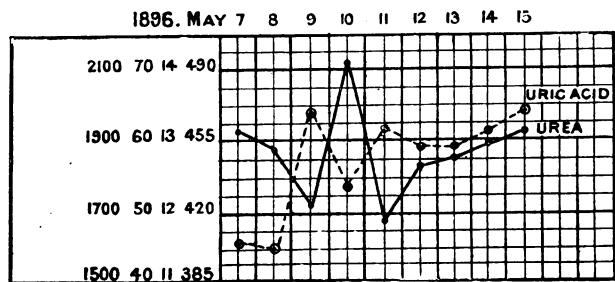


Fig. 4.—Milk and cheese.

tion in 1893, when introduction had not been completely controlled, and when elimination from stores and accumulations was still going on; now here 45 gr. of salicylate of

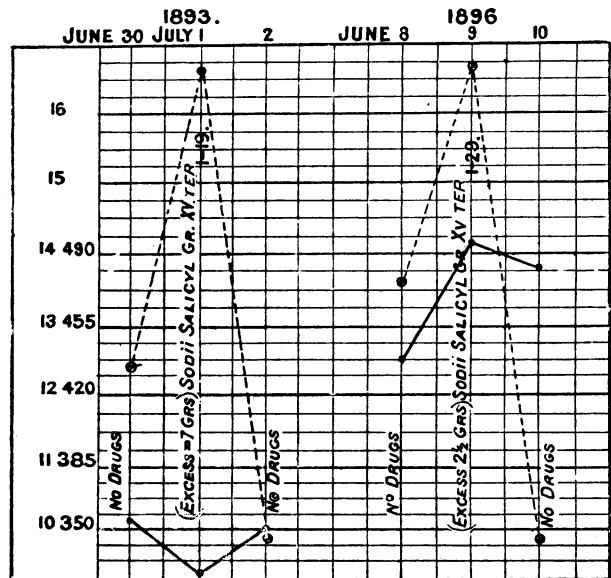


Fig. 5.

sodium caused an enormous excretion of uric acid, bearing the relation to urea of 1 to 19, so that more than 7 gr. of uric acid passed through the blood that day. In 1896, however, elimination from stores had almost ceased and the daily introduction was almost *nil*, and here 45 gr. of salicylate only produced an excretion of 1 to 29, and only 2 1/2 gr. passed through the blood.

I think it may be safely said that if anyone takes an equivalent dose of salicylate of sodium, and gets as the result an excretion of uric acid greatly above the relation to urea of 1 to 30, such person is by no means free from uri

acid or the diseases it may cause, and is either introducing considerable quantities of uric acid with his daily food or has still considerable stores of the substance waiting to be dissolved out of his tissues.

The required alteration of diet is governed by very simple rules, which can be grasped by anyone in a few moments of thought. We have to cut out from "ordinary diet" all articles that contain either uric acid or xanthin compounds that can be converted into it, and we have thus to eliminate all animal foods except milk and cheese. But we must provide nitrogen enough to keep urea constantly about $3\frac{1}{2}$ gr. per pound of body weight per day, and we must therefore replace the animal foods left off by other things containing albumens. Now this can be done chiefly from three sources : (1) milk and cheese ; (2) pulses, as lentils, peas, beans, dholl, etc. ; (3) cereal foods, as wheat, barley, oats, and things made from them. And when we consider that meat contains about 25 per cent. of albuminates, while the pulses contain 22 per cent., cheese 33 per cent., the cereals from 8 per cent. as bread to 12 per cent. as oatmeal, and milk from 3 to 4 per cent., there can be no difficulty in replacing one class of foods by its equivalent in the other, so that urea, nutrition, and strength shall remain unaltered.

The diseases that react to this treatment are practically the whole of those about which I have written, and it will be found that I have not made my claims one bit too large; for uric acid acts in the production of diseases (1) through the circulation, which it controls throughout the body ; and (2) as a direct irritant of fibrous tissues and joints, and the above control of the diet suffices eventually to control its evil activity in both these directions.

The diseases which best and most quickly give evidence of the good effects of this control are the purely functional ones, headache, mental depression, and the high blood pressure which accompanies and causes them ; these are followed at variable distances by anaemia and other blood diseases, albumuria and Bright's disease, epilepsy, gout and rheumatism. On the other hand, it is quite possible, by administering uric acid in any of the forms mentioned above to increase both the daily excretion in relation to urea and the amount that can be swept out by a salicylate. And with this and as its result, there will be a marked increase of all the functional troubles which are due to uric acid in the blood. When the uric acid headache has been properly diagnosed and the above treatment carried out, I look upon cure as almost a matter of certainty, and much the same holds for high blood pressure, mental depression, sleeplessness, and other kindred troubles. Then with regard to Bright's disease, as some of its chronic forms are to be regarded merely as the last stages of unrelied migraine, it follows that the cure of the functional disorder, which is both easy and certain, is equivalent to the prevention of the more serious organic disease.

As regards anaemia, I pointed out in this Section two years ago that the value of the blood decimal varies from day to day with the amount of uric acid excreted in the urine. At that time my blood was much less free from uric acid than at present, and my blood decimal now exceeds its value of two years ago by 10 per cent. or more. And every disease I have written about will react very decidedly to the practical increase or diminution of this substance in the body and blood, and I claim no disease as due to uric acid which will not do so.

DISCUSSION ON THE RELATIONS OF THE MORBID CONDITIONS DEPENDENT ON, OR ASSOCIATED WITH, THE PRESENCE OF STREPTOCOCCI.

I.—G. SIMS WOODHEAD, M.D.,

Director of the Laboratories of the Royal Colleges of Physicians and Surgeons.

SINCE micro-organisms were first recognised as playing an important part in the production of disease, there have from time to time been most curious fluctuations of opinion as to the exact part that the streptococcus pyogenes plays as an etiological factor in certain acute and suppurative diseases. It is not my intention here, nor would it come within the scope of an introductory paper, to give a list of the various

diseased tissues and fluids in which streptococci have been found, nor of the diseases with which they have been found to be associated. This has already been most admirably done by Dr. W. Bulloch.¹ There is, however, a further reason why I should not go into this question this morning—that is, that in many cases it is probable that the streptococcus plays merely a secondary part, and is often a concomitant, rather than a primary, factor in the production of disease. That this is not to be wondered at is evident, when we come to consider how all-pervading streptococci are. They have been described as occurring along with others of the pyogenic organisms in the buccal and oral cavities, on the skin, and in the glands of the skin, of both animals and man ; in clothing, dust, and, in fact, in almost every conceivable position to which animal excretions and secretions can in any way gain access. This being the case, it is not at all extraordinary that streptococci should have been found so frequently in diseased tissues, and that in some cases at least they should for long have been mistaken for the primary cause of the disease rather than as an accessory after the fact. For example, Oertel in Germany, and several observers in this country and America, for long insisted that the streptococcus pyogenes was the etiological factor in the production of false membranes in diphtheria ; and even after Loeffler and Klein had established the position of the Klebs-Loeffler bacillus in relation to this disease, a great amount of confusion continued to reign, and the distinction between ordinary streptococcal angina, true diphtheria, and a mixture of the two conditions—a mixture which undoubtedly often occurs—was seldom, if ever, recognised. Now, however, that such enormous numbers of observations have been collected, the streptococcus is coming to take its true position as far as diphtheria is concerned. Similarly, I am now convinced that many of the processes which at present are looked upon as being merely streptococcal will be found to be mixed infections in which other organisms play a primary or adjuvant part ; the bacillus coli communis being one of the organisms which must in this light be studied along with the streptococcus.

During recent years the tendency in all bacteriological investigations has been to attempt to trace, on the one hand, morphological differences between groups of organisms that have common functions and give rise to similar products, and on the other to ascribe different functional activities to organisms which morphologically are practically identical. Thus there have been described no fewer than six different pyogenic streptococci, to each of which a separate name has been assigned, and which have been arranged in three separate groups. These organisms are almost identical in their microscopical appearances, and their manner of growth is practically the same in all cases. When, however, we come to inquire into the products of these organisms, and to study their relative pathogenicity, the characters of the different organisms at first sight appear to be distinctive. The organisms which may be considered to be in the first group, the streptococcus pyogenes, the streptococcus pyogenes edematis (Flügge) and the so-called streptococcus septicus, have common morphological characters in addition to which they all prove fatal to mice and rabbits when injected into the veins, and in most cases when injected subcutaneously. A second group described as consisting of the streptococcus erysipelatis and the streptococcus septo-pyæmicus are identical in appearance and in growth outside the body with those above described, but they are said to be able to develop less readily in the tissues of the human body, and they are certainly not so fatal to mice and rabbits. A third group is said to contain a single species, the streptococcus articulorum, which, according to Loeffler, appears when injected into the veins of rabbits to have a special affinity for the joints, setting up acute articular inflammation, which is rapidly followed by the death of the animal. How far these are merely "sports" or varieties of one species, can not yet be accurately determined.

It may be well here to indicate generally the type of disease with which streptococci of some form or other are generally associated. In the anginas of scarlet fever,

¹The Rôle of the Streptococcus Pyogenes in Human Pathology, *Lancet*, 1896, vol. i, p. 582.

measles, and rheumatism, they are almost invariably met with, in puerperal fever, in false membranes in association with other organisms, such as the diphtheria bacillus, or the pyogenic staphylococci, in abscess and inflammatory processes, especially those connected with the buccal mucous membranes in various forms of otitis, in peritonitis, often associated with the bacillus coli communis, and wherever superficial pus formation is met with, in furuncles, dermatitis, following or associated with fungi of various forms, pustular skin eruptions, erysipelas and phlegmonous inflammations, especially those of badly nourished patients, or in those in whom there is any interference with the removal of excretions, or where there is anaemia, especially following haemorrhage.

It is evident from the wide distribution of streptococci under normal conditions, and from the great variety of the disease processes with which it is found to be associated:

1. That it must itself undergo great modifications as regards its power of growing and of forming its special pus or inflammation-producing products.

2. That it is so frequently found associated with other organisms in widely different conditions that the modifications mentioned under (1) may well be due in part at least to its symbiotic existence.

3. That it produces even when present in pus, say, as a pure culture, such very different degrees of reaction, when inoculated into different species of animals, and animals in various states of health, that the state of the tissues themselves must play a most important part in determining the life-history and functional activity of the parasitic organism.

We now know that even outside the body a virulent streptococcus may rapidly lose its pathogenic power, and it is only by exercising the greatest care by growing it in serum bouillon, and then passing the organism through rabbits from time to time, that this pathogenic activity can be exalted or even maintained. The exaltation of virulence that has been obtained from comparatively harmless streptococci by using Marmorek's methods is, however, so remarkable, that the discrepancies observed by earlier workers at once become explicable, on the theory that the same organism may at different times adapt itself to a saprophytic mode of life on the one hand, or as the conditions under which it exists become gradually altered, to a parasitic mode.

It is evident, of course, that during the saprophytic life the activity of the organism becomes diverted along the lines most favourable to the reproduction of its species in large numbers, as the agents inimical to its existence are comparatively few and of a different kind from those with which it has to contend during its parasitic existence. It leads, therefore, what may be called a vegetative life, devoting its energies to reproduction and to withstanding the action of light and similar destructive agents.

During its parasitic existence, on the other hand, the organism is waging warfare for its very existence; in its new surroundings, with the different food now at its disposal (proteids of various kinds), and contending against living cells, much of its vegetative activity is diverted to the production of substances which will exert a paralysing influence on the living tissues. The streptococcus is living, as it were, at a higher level, and is forming substances which in its merely vegetative existence it is incapable of producing. We must not assume from this that the micro-organism is still capable of going back suddenly to its saprophytic existence, and of at once reproducing its progeny as rapidly as before. This is not the case; the streptococcus does not grow so easily outside the body as before, and it is only as the higher, or toxin-forming, function becomes modified that the power of vegetation returns in full force. It is not necessary to do more than indicate this point, and I bring it forward merely to show that the different tissue changes set up by the action of the streptococci are merely what might be expected after the experimental evidence of the alteration of function has been carefully considered.

The second point raised for discussion should not detain us for more than a moment—the effect of the growth of other organisms—the diphtheria bacillus, the bacillus coli communis, the bacillus typhosus, the bacillus prodigiosus, etc., alongside the streptococci.

The third point to which I have called attention, the pre-

liminary devitalisation of tissues, may be dismissed with a very few words. Tight sutures, bruising of the tissues, the removal of epithelial barriers as in the case of wounds, where, also, the other tissues are often bruised, the action on the tissues of chemical irritants of various kinds—exhaustion, exposure, haemorrhage, imperfect nutrition and excretion; glycosuria and similar conditions are now so fully recognised by the surgeon as predisposing causes of streptococcal invasion, and others will so readily spring to the minds of my hearers that any further catalogue or description of them is quite unnecessary. This briefly indicates the lines on which I think discussion will prove most useful, and at this point I leave the question in the hands of those, many of them better able to deal with it than I am.

II.—ROBERT MUIR, M.D.,

Assistant to the Professor of Pathology, Edinburgh.

DR. MUIR considered that Marmorek's work on the variations in the virulence of individual cocci showed that the artificial distinctions between the various kinds of streptococci will not hold. He compared the erysipelas bacillus in its clinical aspect to the organism of croupous pneumonia; both can on occasion become pyogenic, but each requires to be worked up, so to speak, to a special stage of virulence to produce pus. The staphylococcus, on the other hand, is the pus-producing organism *par excellence*. Dr. Muir did not agree with Dr. Woodhead's distinction between the different kinds of pneumococci; he held that the only real test of the identity of two organisms was to immunise an animal with one, and to observe if it became resistant to the other.

III.—F. W. FORBES ROSS, M.D.

DR. FORBES ROSS said that Dr. Woodhead's remarks on the bacillus coli communis being probably primary to the streptococcus showed that in most cases of disturbance of the alimentary canal the streptococcus made its appearance secondarily to the other organisms, which had previously brought about conditions favourable to the action of streptococcus. He thought that Dr. Muir's work on pseudo-tuberculosis tended greatly to clear up the doubt which may exist in cases of tabes mesenterica with enlarged spleen, some cases being undoubtedly tuberculous, others not so being probably cases of other bacterial infection from the alimentary canal. As regards Dr. Muir's remarks as to immunisation, this was probably also correct, seeing that in some cases the clinical history seems to tend that way.

SOME NOTES ON ASCENDING DEGENERATION (SO-CALLED) AND ON THE CHANGES IN NERVE CELLS CONSEQUENT THEREON.

By ROBERT A. FLEMING, M.D., F.R.C.P.E.

THIS paper partakes more of a short summary of results than a detailed account of ascending degeneration. Full reference to past researches, many of which are most contradictory, is impossible, and it is even difficult to find place for a sufficient account of the premises upon which my conclusions are based. I propose to consider:

I.—“ASCENDING DEGENERATION.” IN WHAT DOES IT REALLY CONSIST?

I do not here refer to septic or infective inflammation, but to the changes found in the central end of a nerve after section or ligature. Dickinson¹ in 1868 records wasting of the sciatic nerve after amputation. Hayem in 1876 describes diminution of the anterior nerve roots, the nerve fibres being replaced by connective tissue, the myelin in some fibres broken up and the peripheral nerves undergoing parenchymatous neuritis. Déjerine and Mayor² in 1878 describe no changes in the nerve or in the connective tissue, save in the neuroma itself. Hayem and Gilbert³ in 1884 describe the

¹ On the Changes in the Nervous System which follow the Amputations of Limbs. *Journal of Anatomy and Physiology*, 1868.

² “Recherches sur les Altérations de la Moëlle et des Nerfs du Moignon chez les Amputés d'ancienne date.” *Gaz. Méd. de Paris*, 1870.

³ “Modific. du Système Nerveux chez un Amputé.” *Arch. de Physiolog.*

nerves of stumps after amputation as very markedly reduced in size, the fibres diminished in number and also in calibre, not merely the myelin being less in amount, but the axis cylinders shrivelled, and connective tissue taking the place of degenerated fibres in the bundles. Some nerve fibres are very thick, the myelin being increased in amount, and the axis cylinders granular. The numbers of these vary in different bundles. There are also innumerable small fibres with little myelin, and thick axis cylinders, the myelin staining well with osmic acid. These small fibres are grouped in bundles, or separated by connective tissue. The small bundles containing these fibres are *in toto* larger than an ordinary nerve fibre, each containing a varying number of the small fibres. They think these are evidences of nerve regeneration. Krause and Friedländer⁴ (1886) find Wallerian degeneration, but the anterior roots are normal, the posterior only altered as far as the ganglia. They think that sensory fibres have a peripheral trophic centre in the touch corpuscle.

I might quote many others, but coming nearer to the present time we find Marinesco⁵ recognises marked changes in the nerves of a stump after amputation; fibres shrunken, many small and resembling naked axis cylinders. Most fibres he thinks degenerate, and the degeneration is Wallerian. Redlich⁶ in 1893 finds degenerated fibres in the anterior roots, and little in the posterior till 5 to 10 weeks after the operation. Other writers find some changes in the central end, and Homen⁷ in 1894, as the result of amputating the limb in dogs at different ages, and killing at different intervals of time extending from days to years, finds that younger dogs show more marked changes than older ones.

In a dog, 8 months old, and 3 weeks after amputation, the greatest number of sciatic nerve fibres were unaffected, amongst those altered some are of normal size, some smaller, and some very specially so. Increase of nuclei in the sheath of Schwann was noted especially in the small nerve fibres. Some loose connective tissue surrounding the fibres was found, and this might press seriously upon them. Many of the nuclei are broad and seem to have a larger amount of surrounding protoplasm than usual. Myelin is granular, and axis cylinders are often interrupted at several places. These changes appear in one to three weeks, and are found in small bundles of fibres. There is no change in the epineurium. In another dog, 1 month old at the time of amputation and killed 1 year after, motor and sensory fibres are very different indeed. The motor fibres are only to a small extent affected with granular myelin, etc., while the sensory fibres are represented by a greater number of very small fibres than usual, and are further apart than is normally the case. These stain in the usual way by Weigert's method, whereas the other fibres stain less sharply and their myelin is granular.

Some writers, such as Erlenmeyer, Genzmer, Homen, Varnclair, etc., think ascending degeneration is a simple atrophy; other writers, as Krause, Friedländer, etc., think the myelin suffers, and the axis cylinders escape. In fact, we may state that the degeneration is not believed to be Wallerian, and it is generally held to be an ascending change. Forel, Ramon y Cajal, etc., think it is really a descending degeneration consequent on the injury sustained by the trophic cell, following on the section or other lesion. Durante denies this descending theory and brings in support the following argument, that in ascending degeneration of the pyramidal tracts, degenerative changes cannot be traced beyond the decussation in the medulla; and that the changes become less and less marked, while the trophic cells need not suffer at all, and often do not.

What then, are we to believe? Is there any explanation for the diversity of opinion expressed? This is no trivial question, because it is one which appeals to every surgeon when he amputates a limb or cuts or stretches a nerve.

I wish here to allude to two points. First, the methods adopted for operation by some of the observers, and the fix-

⁴ Ueber Veränderungen der Nerven und des Rückenmarkes nach Amputation. *Fortschr. der Medizin*, 1886.

⁵ Modifications des Nerfs et de la Moelle chez les Amputés. *Berlin. klin. Wochensch.* September 26th, 1886.

⁶ Zur Kenntnis der Rückenmarkes Veränderungen nach Amputation. *Centrabl. f Nervenheilk.*, 1893.

⁷ Die Krankhaften Veränderungen der Nerven nach Amputationen. *Atlas der pathologischen Histologie des Nervensystems*. Von Babes u. Blocq 1894, Lief. 2.

ing and hardening of the specimens may be blameworthy. The most rigid antiseptic precautions are absolutely necessary, and in using dogs as subjects this presents extreme difficulty, because dogs pick out stitches, tear open wounds, and very readily induce suppuration. If we consider what is really included in the term of traumatic ascending neuritis, we have something which will throw light upon the discrepancies just referred to. An ascending neuritis may be very acute, rapidly spreading up to the cord affecting ganglion cells in the grey matter, and even extending up to the medulla, producing a fatal result; or it more commonly may be an acute, subacute, or extraordinarily chronic, but generally less disastrous, inflammation, the result of a less potent agent. How to produce the severe form we do not know; very probably it is microbic, but the less extensive variety is much more easily obtained than is often stated. Howell and Hubert rarely got it in dogs, as the result of nerve sections, crushing, etc. Traube found it only confined to nerves. Hayem got it by tearing out the sciatic of dogs; whereas other experimenters, as for example, Vulpian, very seldom, if ever, found it at all. A neuritis of this kind is never induced without some means of admitting an organism or a more or less virulent toxin circulating in the blood, such as that of gout, rheumatism, and probably the toxic agent in diphtheria, etc., and a septic wound is the common cause of the organismal form. As Strümpell, Kast, and Rosenbach consider most probable the neuritis resulting from an extra nerve injury is due to thickening of connective tissue, and is a degeneration caused by pressure and not a true inflammatory condition at all. It is a well recognised fact that a nerve, if its sheath be not damaged, can, without much injury, be bathed in pus, and may in fact only eventually show evidence of involvement by the pressure of the resulting cicatricial tissue, when the pus becomes absorbed or is evacuated. I need not do more than refer to the fact that there is little and certainly no very distinct connection between the intra- and extra-funicular lymphatics. If dogs are apt to tear out stitches, cats are far worse, and therefore the results obtained by the experimental work on the nerves and spinal roots in these animals are open to some adverse comment.

In my own series of experiments, I used no antiseptic except boiling water, and I rejected every case where there was not union by first intention, or where there was any cheesy material in the wound. So far, the operations on dogs' sciatics which I have performed or seen performed, number fifteen in all (on fifteen different animals) and of these, carried out with the utmost care so as to prevent the entrance of septic organisms, only about one in four of the wounds healed by first intention, and the central end of most of the dogs' nerves showed far more signs of a degenerative or inflammatory process than the rabbits. A rabbit never picks out stitches from the hind limb, and if well cared for, there is little tendency to septic mischief. Hence I believe rabbits are more satisfactory for such experimental work than dogs.

There is one observation which I think most neurological workers will confirm, namely, that nerve fibres if slightly degenerated require much more careful and painstaking fixing and hardening than normal ones, so as to eliminate bead-like swelling of myelin, etc.

The second point to which I wish to refer is, with regard to the possibility of distinguishing between a nerve inflammation and a nerve degeneration. I believe an inflammation means an exudation with leucocytes, in addition to the degenerated fibres met with in Wallerian degeneration. It should also be noted that not a few of our most trustworthy authorities have seen fit to change their opinion as to the nature of ascending degeneration after performing a second series of experiments, thereby testifying to the difficulty of obtaining dependable data.

My own results are obtained from examining the central ends of divided or ligatured nerves of over seventy rabbits and dogs—mainly the former—these results are in brief. First, that in process of time a slow atrophy of "motor" fibres occurs. Secondly, that certain "sensory" fibres degenerate centrally, possibly because severed from their peripheral trophic centres. Thirdly, that the minute fibres found in a normal nerve undergo very marked change. Fourthly, that distinctive connective tissue increase occurs.

The first and second points have been fully discussed by

other writers and I wish to direct special attention to the third and fourth. Let me preface these remarks by describing the appearances noted in the ulnar nerve of a stump, nearly ten years after amputation. The patient was aged 27, and was therefore 17 when he lost his arm. Just above the terminal neuroma the fibrous tissue of the perineurium is greatly thickened, and in the endoneurium not merely are the broad septa increased, but between little groups of fibres, numerous connective tissue nuclei may be seen. These little groups of fibres are specially interesting. They do not occur in large numbers in all the bundles. In one funiculus there are very few groups of connective tissue nuclei, and on careful observation nearly all the fibres are seen to be large fibres. Where nuclei do occur in numbers a few fine fibres are seen. In another funiculus very near the preceding one, there are a very great many more clusters of nuclei and these are seen to be associated with fine medullated fibres arranged in groups. But in both of these funiculi, the fine fibres are not normal when viewed with the high power.

The bundle last described ought to contain large numbers of fine fibres. The other bundle evidently ought not. Weigert-Pal specimens show these little fibres manifestly degenerated, that is to say the myelin is segmented or absorbed, the axis cylinder stained feebly or absent altogether, while the nuclei are proliferated.

The paraffin specimens stained with haematoxylin and eosin, show the striking increase in nuclei, where these little groups of fibres are situated, the disappearance of many of the fine fibres—the nuclei just referred to taking their place—and the loss of axis cylinders in not a few of these fibres, the outline of whose sheath is still distinguishable. Longitudinal sections through these little groups demonstrate beyond any doubt that the bulk of these nuclei are, in reality, long spindle-shaped connective tissue nuclei, and not merely proliferated segmental nuclei.

The obvious conclusions are that the connective tissue has replaced these fine fibres to a great extent—many of these being shrivelled beyond recognition, and many minus axis cylinders, and that most of the proliferated segmental nuclei have disappeared.

On careful examination of the various fasciculi in the specimen, I was struck by the fact that though in the ulnar nerve there is generally a considerable number of very fine medullated fibres, here there were extremely few, and many fasciculi were composed almost exclusively of large fibres which were much more healthy. These fine fibres, as Gaskell has pointed out, are probably designed for the supply of vessels, and they mostly leave the cerebro-spinal axis in certain regions alone, pass to the sympathetic ganglia and from them return to peripheral nerves. These fibres, scattered all through the funiculi in which they occur, seem to find their way to the periphery of a fasciculus at different levels, and probably do so near their points of distribution.

In support of this theory, I find the vessels in the ulnar nerve have suffered right up to the highest part which I possess of the nerve. The perineurium is thickened apparently further than the limit of my specimen. There is a very slight diminution, but still a diminution in the total number of the degenerated groups in any funiculus, estimating the number from below upwards, and the changes in these fine fibres might be produced by the thickened perineurium and septa. The smaller arterioles and capillaries in the endoneurium show most marked increase in number of the endothelial nuclei of the intima, of the nuclei of the media, and to a less extent of the adventitia. On careful observation there is no question that when in a funiculus the minute fibres are degenerated, the vessels in the neighbourhood have suffered in this way, whereas in the few funiculi which show most of these fibres unaffected the vessels have escaped. These nuclear changes are less marked in the vessels of the perineurium and are only found in parts of the epineurium. There seems to be no doubt that in the sensorimotor nerves of rabbits at least, and certainly also in those of man, the bulk of the vasoconstrictor fibres are medullated. It requires considerable skill and painstaking examination of transverse sections of many nerve trunks before such an assertion can be made, but I believe I am justified in making it. It is also sometimes difficult to distinguish non-medullated

nerve fibres from fibrous tissue. Longitudinal sections through the fine bundles in the nerve above the neuroma show that the nuclei are of far greater length than those found in grey fibres, and although it may be argued that the grey fibres have shared the fate of the white, still my experimental results tend rather to prove that most of the nucleated fibres are those of connective tissue. Determined to ascertain if the central ends of the divided nerves in my experimental sections would lead to the same conclusion with regard to the fine fibres, I made careful observations in each case. There is a fairly rapid development of nuclei and of connective tissue fibres between and around the fine medullated fibres, and this change is recognisable by the end of 4 to 7 days, and very marked by the end of the third week. A lantern slide to illustrate the appearance of this connective tissue increase at the end of the 23rd day after ligaturing a rabbit's sciatic was shown. It represents, in transverse section, the connective tissue fibres forming strong septa, evidently capable of exerting hurtful pressure on the fine fibres around them.

Another slide shows by way of contrast a longitudinal section of the same nerve on the healthy side. The relationship of the fine fibres to the connective tissue strands can be made out, but the strands are not nearly so thick as in the affected nerve. There is no corresponding thickening of the perineurium after a ligature 23 days old, therefore I can hardly argue that it is owing to a general connective tissue increase that these fine medullated fibres have suffered. It is much more probable that it is because the fine fibres have sustained damage that this local connective tissue increase has made its appearance. I ought to state that I have definitely satisfied myself that the connective tissue trabeculae supporting the fine fibres are much better developed than those supporting the larger fibres, and hence it is easy to understand how so great a proliferation of connective tissue can take place. Supposing, then, that a section of one of these fine fibres means that it is cut off from a trophic centre not necessarily its only trophic centre this might cause the change in question—or, another theory—these fine fibres are influenced from two stations, one at either end—that is to say they conduct almost certainly both ways—therefore, a peripheral stimulation or irritation of these fine fibres, produced at the site of section, may account for the phenomena.

There are no vessel changes in the central end of the rabbits' sciatics, as there were in the neuroma; but, if the vessel changes depend on a nerve cause, the fine fibres supplying the vessels seen in the central end of the nerve are still undamaged, whereas in the neuroma, the age of the lesion would mean contraction of the fibrous tissue replacing degenerated fine fibres. In this way previously healthy fine fibres in the immediate vicinity would be interfered with, and thus the vessel changes for some distance up the ulnar nerve in the neuroma might be produced. Probably similar changes would appear in time after experimental sections, but only after months or years. To sum up. The fine fibres appear to suffer first and most, connective tissue replacing the fibres severed, and these fibres degenerate a certain distance upwards at least.

Unfortunately I cannot supply any exhaustive evidence as to how far these fine fibres degenerate. A research into the changes resulting in the cells of the chain of spinal sympathetic ganglia, in the cells in the medulla, where probably the vasoconstrictor centre is situated, and finally the presence of degenerative changes in the connecting links between sympathetic ganglia, the medulla, and the peripheral nerves would require to be instituted before the question could be finally settled.

It is upon this very subject that I am at present working, and I had hoped to have some results ready for this meeting. The research is, however, not concluded, and all I can at present state is, that the incomplete series of experiments appear to bear out the truth of the observations just made.

II.—THE CHANGES IN NERVE CELLS.

The cells with which this paper deals are those of the ganglia on the posterior nerve roots and the multipolar cells of the anterior cornua of the cord. I need say nothing of the structure of these in the rabbit, the dog, or man, because that is

familiar, and space will not permit of a digression on the methods of fixing; but I may state that what I believe to be my best results were obtained by using a saturated solution of corrosive sublimate (in a 0.75 per cent. solution of common salt in water) diluted by adding an equal quantity of water and the mixture heated to the temperature of the tissues to be fixed. With this solution I have succeeded in getting fairly satisfactory nuclear networks and no evidence of shrinkage of the cell body. I would further add, that faithful adherence to the same fixing and hardening methods, and the same methods of staining is calculated to exclude error and detect artificial appearances in a far more satisfactory manner than when using several methods, precluding proficiency in any one of them. The stains used for most of my work are toluidin blue and eosin—a method for which I was originally indebted to Dr. Gustav Mann.

Little has been done in the way of recording changes in the nerve cells of the spinal ganglia after a nerve section or ligation. Much more has been written by Nissl, Marinesco, and others upon the changes in the cells of the anterior horn. The utmost difference of opinion exists as to which group of these cells suffer or whether any of them really suffer at all.

By comparing the normal with the operated side, I was able to eliminate the risk of my results being purely or mainly artificial. The changes which I noted in the cells were:

1. The cells of the ganglia on the posterior nerve roots undergo definite changes as the result of nerve section or ligation, and do so at a much earlier period than the multipolar cells in the cord—beginning probably as early as the fourth day and certainly by the seventh day.

2. That one of the very first changes observed in the cells of ganglia and anterior cornu is a diminution in the size of the nucleus—in proportion to the size of the cell and that, sometimes, but not in all cases—nucleoli also become smaller and very frequently the nuclei take up an eccentric position, sometimes even bulging the cell wall.

3. That in both sets of cells Nissl's granules, otherwise known as the chromatic granules, are either smaller in size, fewer in number, and scattered through the cell body tending to be most numerous round the nucleus, or else they are grouped together in large masses round the nucleus, leaving the periphery of the cell quite clear.

4. That pericellular lymph spaces may become enlarged, especially in the ganglia cells, and where the enlargement is very marked, the cells become proportionately smaller in size—although an actual atrophy may also occur. In several of my specimens I found large vacuoles—not the vacuoles described by many writers as occurring in the cells of the cord and cerebral cortex, which are probably to some extent artificial—but big vacuoles more resembling distended pericellular lymph spaces. They differ however inasmuch as they are surrounded by the remains of cell protoplasm containing chromatic granules.

5. That in the multipolar cells not merely are there these changes in position and size of nuclei, and arrangements and number of chromatic granules, but there is as a later phenomenon, marked disintegration of cell protoplasm, well seen in some of my specimens. This disintegration has been described by Marinesco as occurring in certain cord lesions in man. It consists of patches—which with toluidin blue and eosin, are whitish in colour and surrounded by masses of chromatic granules.

This stage of disintegration follows only at a very late stage in the ganglion cells of the posterior nerve roots. It should however be stated that a varying number of normal cells occur in abnormal ganglia, and that a very few abnormal cells occur in normal ganglia. The changes in the cells most commonly observed in normal ganglia are an aggregation of chromatic granules round the nucleus and more rarely in eccentric position of nuclei. By normal ganglia I mean ganglia of presumably healthy rabbits never submitted to any experiment at all, as well as ganglia unaffected by the experiments performed. The proportion of such abnormal cells in a normal ganglion rarely exceeds 2 per cent. of the whole. Vacuoles may also appear, but much more rarely, and their presence is quite exceptional.

I wish very specially to draw attention to the fact that the spinal ganglion cells have impulses conducted towards them in health by the very fibres which have been severed, and

therefore they should suffer at an earlier date than multipolar cells whose axis cylinder processes conduct in an opposite, that is, a centrifugal direction.

I have long series of measurements of cells and nuclei in a considerable number of experiments, but it seems out of place to introduce these in this paper. The tables will in due course be published in full. I should state, however, that the cells in the anterior cornua found to be affected were not confined to any special group, and that not infrequently one or two of the cells on the "normal" side suffered similar changes.

In no case did I find any evidence of degeneration in the anterior roots, and I wish to hold over the description of the posterior roots till the full details of my experiments are published as it would add greatly to the length of this paper. The abdominal sympathetic ganglia show also changes similar in certain respects, but of them I cannot yet speak with confidence.

The diminution in size of the nuclei is a point not previously recorded, and yet it is a result upon which it is possible to count with considerable certainty. If, however, there is any inflammation, pus, etc., at the site of lesion, the nuclei may swell up, becoming greatly distended. This appearance is by no means common in my experiments.

When examining the cord of a case of peripheral neuritis—in which the one arm was much more paralysed than the other—the nerve cells in the anterior cornu on the affected side showed diminished size of nucleus and cells as compared with those on the less affected side, and the whole nucleus had a crenated appearance.

It is extremely interesting to find the same changes in the multipolar cells in at least one case of peripheral neuritis as after-experimental ligation or section.

The object of this paper is to bring, first, the changes in the minute fibres of the central end of a divided or ligatured nerve, and secondly the changes in the size of nerve cells and cell nuclei, before the notice of the members of the British Medical Association.

In conclusion, I wish to draw attention to the practical bearings of these observations. After a lesion of axis cylinder processes, those trophic cells whose processes conduct nerve stimuli towards the cell suffer first. No trophic cell can escape injury if its axis cylinder process is damaged. The minute fibres, probably mostly vasomotor, are very vulnerable, and as I hope to be able to prove in a future paper, their trophic cells suffer in a very similar manner to trophic sensory and motor cells.

In peripheral neuritis, sometimes the vasomotor cells are attacked, sometimes only the sensory and motor. Where the vaso-motor suffer seriously death probably must result; hence the number of fatal cases which show changes in the vessels of the affected nerves, since attention was first drawn to this phenomenon. It is impossible to say how vasomotor cells become more vulnerable to the toxin, or what the chemical change in the cells may be, but surely there is some hope that in any severe case of multiple neuritis therapeutic agents may be found which might increase the power of cell resistance to the toxin, or help them when in the toils of conflict. It seems to me that we do far too little for the cells in nerve lesion, although it is not my design or desire at this time to speculate upon the best means of carrying out this suggestion.

In conclusion, I wish to tender my thanks to Sir Thomas Grainger Stewart and to Professor Hermann Munk of Berlin, in whose laboratories the work referred to has been conducted.

A CASE OF HYPERTROPHIC PULMONARY OSTEO-ARTHROPATHY.

By F. H. WESTMACOTT, F.R.C.S.

(With a Post-mortem Report by Wm. THORBURN, B.S., F.R.C.S., and F. H. WESTMACOTT.)

The case described was one of the rare disease first described by Marie in 1890, and called by him "hypertrophic pulmonary osteo-arthropathy" on account of the close association which appeared to him to exist between the abnormal condition of

the lungs and the extensive changes in the periosteum of the bones constituting the limbs.

In the BRITISH MEDICAL JOURNAL of June 3rd, Mr. Thorburn had recorded three examples of the affection; one, a lad, remained under observation until his death, which took place in September, 1895, from asthenia of general amyloid disease, his clinical symptoms undergoing no material alteration. The *post-mortem* examination, which was very complete, showed almost universal osseous and articular change. There were evidences of old tuberculous disease in the spine, lungs, right suprarenal capsule, and a healed focus at the tubercle of the right tibia. The skull was remarkably sclerosed, devoid of diploe, and roughened internally—the thickness at the pterion being $\frac{1}{4}$ inch, while at the frontal and occipital bones it was $\frac{1}{8}$ inch as divided by the usual *post mortem* section. In the facial bones, ribs, sternum, and vertebrae, except in the carious region and clavicle no changes were observed. The limb bones were covered with a rough, finely porous layer of subperiosteal bone; their compact tissue being sclerosed to a greater or less extent in different bones, and their medullary cavities encroached upon by new bone. These osseous deposits were especially marked in the long bones and at the attachments of muscles and fascia, and in nearly all cases was this new deposit confined to the diaphysis. The nutrient foramina were increased both in size and number. Finally the carpal, metacarpal, and phalangeal bones of the hand presented the usual subperiosteal deposits and cartilaginous erosions. The larger joints of the hip and shoulder contained an excess of synovia, but the synovial membranes presented no definite changes. The joint cartilages were almost invariably eroded as if from atrophy, the erosions selecting the margins of the cartilages, and, on contiguous surfaces, often lying, not opposite to one another, but alternately. The erosions of the heads of the humeri and femora were symmetrical in an extraordinary degree, affecting their margins and extending on to the articular surface at corresponding situations and to a similar extent. In the wrists, ankles, radio-ulnar, carpal, dorsal, and other small joints, erosions of cartilage, principally marginal, were also found. The general condition was a higher symmetrical and almost universal osteoperiostitis of the limb bones, with a trophic erosion of the cartilages of their joints. The viscera indicated a somewhat extensive but much subdued tuberculosis. The liver, which showed advanced amyloid disease, weighed 8 lb. 2 oz., while the spleen, showing similar changes, weighed 1 lb. 3 $\frac{1}{2}$ oz. The right suprarenal capsule was larger than the left, hard, and on microscopic section showed tuberculous changes. (There was no bronzing of the skin during life.) There can be little doubt as to the sequel of events leading to the results which have been described by several observers. The primary and essential lesion of hypertrophic pulmonary osteo-arthropathy is clearly a widely spread and very chronic osteoperiostitis affecting ultimately most if not all of the bones, but commencing in the extremities and always most marked at the distal ends of the limbs. The diaphyses are attacked rather than the epiphyseal ends of the bones. The joint lesions are doubtless secondary, the cartilaginous erosions are clearly atrophic, and they recall the cartilaginous changes of chronic osteo-arthritis, but differ materially in that they are unaccompanied by any evidence of proliferation, as in the latter disease effusion into the joints is only occasionally present, eburnation of exposed bone and formation of periarticular osteophytes which are characteristic of osteo-arthritis are however absent. The ultimate cause of this inflammation of bone is, however, still obscure. Marie attributed it to decomposition of secretion in dilated bronchi or pleural collections of pus with absorption into the system of the resulting toxins, and he suggested that these toxins then excited a periostitis or arthritis owing to their having an "elective action" upon the bones and joints. He compares the disease to the "pseudo-rheumatism" of Bouchard and to gouty intoxication. Bamberg adopts a similar view, and compares the periostitis with that due to poisoning by phosphorus or arsenic. This somewhat complicated theory is, however, incompetent to explain cases such as the one described, in which there is no accumulation of decomposing material.

In 1893 one of us suggested the disease might be a widely spread and very mild tuberculosis of bone, the deduction

being made chiefly from clinical observation, and the present case appears to endorse that view. It is, however, too early as yet to give any strong expression of opinion.

FILARIA SANGUINIS HOMINIS IN THE SOUTH SEA ISLANDS;

WITH PHOTOMICROGRAPHS OF A FILARIA FROM TONGA AND THE FRIENDLY ISLANDS;

By Surgeon V. GUNSON THORPE, R.N., M.R.C.S., F.R.M.S.
Up to within a quite recent period, the etiology of the elephantiasis of the South Pacific islands appears to have been uninvestigated. Judging from its analogy to the disease as seen in India, the probabilities were that a species of filaria would be found in the blood of the natives of these islands in which the disease is endemic; but the possibility that this filaria might not be *F. nocturna*, was pointed out by Dr. Patrick Manson in his paper on Elephantiasis Arabum in the South Sea Islands.¹ A filaria has indeed been found in the blood of the natives of several islands, which however in its general appearance does resemble *F. nocturna*, though it exhibits no "filarial periodicity," and the measurements taken differ somewhat from those laid down as the dimensions of this species of haematozoa. But, as will be shown, these facts do not *per se* justify the establishment of a new species; so, for the present, we must consider the filaria of the South Sea Islands as identical with the *F. nocturna* of India and China. The major portion of the observations on which this paper is founded was made during the survey of Tonga or the Friendly Islands by H.M.S. *Penguin*, but a flying visit to Fiji enabled me also to make an examination of the blood of a few of the natives of this latter group of islands, had I will deal with these last first.

I am indebted to the Hon. Bolton G. Corney, Principal Medical Officer at Suva, Fiji, for his courtesy in allowing me to examine a number of Fijians in the hospital at that port, in August, 1895. One evening only being available, the observations were necessarily limited, but twenty-four slides of blood were prepared, taken between 8 and 9.30 P.M. Of these slides, sixteen were from men with no elephantoid disease, of these four exhibited filariae. Four slides were from men with elephantiasis of various parts of the body (arm 1; varicose groin glands 1; scrotum 2) in one of these cases filariae were present. Four slides were prepared from women, with no elephantiasis, one of whom showed filariae in her blood. These results would appear to indicate that 25 per cent. of the natives of Fiji are affected with filariasis. The observations are in themselves too few to establish such a conclusion, but I was unexpectedly enabled to confirm them, from the examination of one hundred slides of blood prepared by the late Dr. J. A. Offord, of the Suva Hospital between 8 and 9 P.M. (November, 1894, January, 1895) which were kindly lent to me by Dr. Corney. Twenty-four of these slides (which were also carefully labelled) exhibited filariae, which agrees closely with my own result.

As regards the Friendly Islands they are divided into three great groups: the Tonga, the Haapai, and the Vavau groups, besides other dependency islands. Tongatabu is the chief island of the Tonga group; Lifuka and Nomuka the two largest islands of the Haapai group; whilst the large island of Vavau gives its name to the third group. Intercourse between the inhabitants of these islands is frequent, and they will often travel as far as Samoa, which is known to be a hotbed of elephantiasis. Between August and December, 1895, the blood of 214 adult Tongans was examined, children and very young persons being excluded. At first the examinations were made at night only; but in October, considering it expedient to make a few control observations in the daytime, I found to my astonishment, that the filariae exhibited no periodicity, but were swarming in the blood practically in as great numbers as at night. The parasite moreover possessed a well-marked sheath, and in general appearance resembled *F. nocturna* (see Figs. 1, 2 3). Ninety-six natives were examined both day and night, and with two exceptions, all those with filariae in the blood at night exhibited them in the daytime in equal numbers, and *vice versa*.

The first exception was an old woman at Nomuka, who on each of two occasions showed a single parasite only in the drop of blood on the slide at night, but I failed to find any in the daytime. The second was an elderly man at Lifuka, in which the condition was reversed, a single parasite only being seen in the morning, but none at night. He also showed a single filaria in the drop of blood examined at 5.30 P.M. These two cases do not vitiate the general results, as I think they can probably be explained by the approaching death of the parent worm.

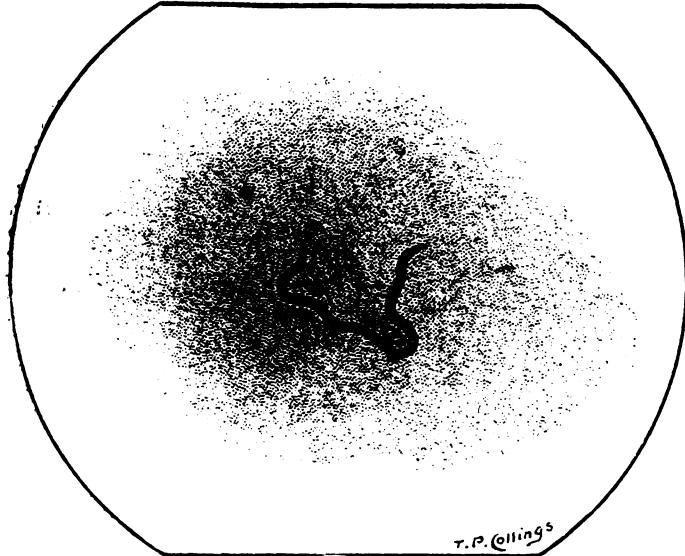


Fig. 1.

DESCRIPTION OF THE FILARIA OF THE TONGA ISLANDS.
After submitting stained and mounted specimens to Dr. Manson for his criticism, we have come to the conclusion that no sufficient grounds exist for regarding this filaria as a new species, in spite of the absence of periodicity, and

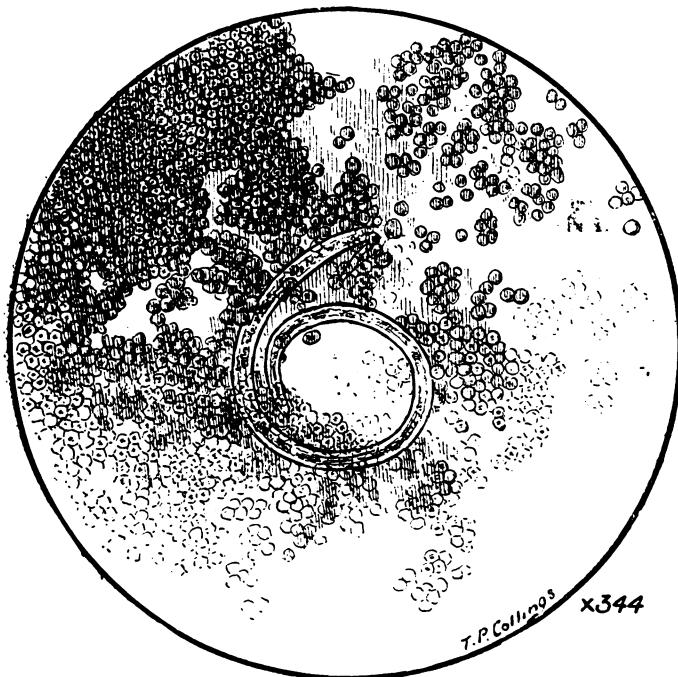


Fig. 2.

certain differences in measurement of its size; and that therefore we must consider it to be *F. nocturna*, the periodicity of which has been altered and modified by the habits of the natives of the Tonga Islands. The average length of the

living parasite is about $\frac{1}{10}$ inch, but varies from $\frac{1}{10}$ inch to $\frac{1}{5}$ inch, a common measurement being $\frac{1}{7}$ inch.³ Stained and mounted specimens undergo a certain amount of shrinkage, and average about $\frac{1}{10}$ inch in length. The average breadth is about $\frac{1}{100}$ inch, but slightly enlarges at the cephalic end, and the caudal extremity gradually tapers off into a sharp pointed tail. The following measurements were made from a single living specimen. Length, $\frac{1}{10}$ inch; breadth, cephalic extremity, $\frac{1}{100}$ inch; body, cephalic $\frac{1}{10}$ th, $\frac{1}{1000}$ inch; middle $\frac{1}{10}$, $\frac{1}{100}$ inch; base of the caudal extremity, $\frac{1}{100}$ inch. It would thus appear that the Tongan variety is somewhat smaller than the same species found in other parts of the world. In all other respects, in the possession of a sheath, and of a preputial cephalic collar, and in the existence of a V-shaped organ, its anatomy resembles that of *F. nocturna* of India and China.



Fig. 3.

The following table gives the proportion of natives affected with filariasis in the four large islands of the group. To

TABLE I.

	Ton-gatibu.		Nomuka.		Lifuka.		Vavau.		Totals.		
	Number Examined.	Filaria.	Number Examined.	Filaria.	Percentage.	Number Examined.	Filaria.	Percentage.	Number Examined.	Filaria.	Percentage.
<i>Males.</i>											
Day and night.....	7	3	—	—	—	25	12	—	23	12	—
Day only.....	3	0	—	—	—	3	0	—	1	0	—
Night only.....	31	11	—	—	—	9	3	—	6	5	—
Totals	41	14	34.1	—	—	37	15	40.5	31	18	57
<i>Females.</i>											
Day and night.....	4	3	—	—	—	26	7	—	11	3	—
Day only.....	3	0	—	—	—	6	0	—	0	0	—
Night only.....	17	2	—	—	—	1	—	—	7	2	—
Totals	24	5	20.8	—	—	43	8	18.6	18	5	28
Totals for whole population	65	19	29.23	80	23	28.75	49	23.47	20	4	20

² I never came across any specimen as large as $\frac{1}{5}$ inch, the average measurement of the *F. nocturna* of China and India.

obviate any misunderstanding, I may state that in most of the cases in which filariae were found in the blood in the daytime, I took extra trouble to confirm their presence at night, but many natives were examined at night only, whom it was impossible to get hold of in the daytime on account of their occupations.

From the preceding table it will be seen that 32.24 per cent. of the total inhabitants of the Friendly Islands have filariae in their blood, and of these, 41.47 per cent. of the male, and 19.9 per cent. of the female population. The percentage in the different islands differs considerably, the probable cause of which, as well as of the difference between the sexes, I shall consider later on.

TABLE II.

Time.	Tubon (male).	Saen (male).	Kesaiā (female).
9.30 A.M.	—	22	—
10.0 "	21	—	80
12.0 NOON	9	27	—
2.30 P.M.	16	—	—
5.30 "	17	—	—
6.30 "	—	16	—
8.30 "	30	—	—
10.0 "	—	—	56

As regards the number of filariae on any given slide, I chose two men and one woman, natives of Nomuka, for purposes of observation. The size of the drop of blood selected was sufficient to spread out in a moderately thin layer beneath a $\frac{1}{8}$ inch diameter circular cover-glass, and the number of parasites in it was carefully counted.

Tubon suffered from lymph-scrotum, and periodic attacks of elephantoid fever. Sam and Kesaiā had no elephantoid disease. The blood of the latter is remarkable for the large number of filariae in it. Another native (a male) showed 14 filariae in one field only (of a 1-inch objective) of the microscope.

Dr. Manson, in his paper mentioned above, points out the liability to implication of the arms and breasts, which is undoubtedly a peculiarity of the disease in these islands, and appears to differentiate it from the elephantiasis of other parts of the world. Among the natives examined a certain number presented symptoms of elephantoid disease. In Tongatābu, two men, with commencing elephantiasis of the leg, both with filariae in their blood, and one woman, with no filariae in her blood, but whose forefinger, somewhat resembling an old strumous dactylitis, was enlarged at the base, and considerably shrunken at its distal extremity, presented themselves. In this latter case, I was assured that the condition of the finger had only appeared during the last two years. That this condition was due to lymph stasis caused by the dead body of a previously aborting parent worm being imbedded at the base of the finger, is at least doubtful. At Nomuka, 7 cases presented themselves; one of lymph scrotum, with filariae in the blood; one of elephantoid disease of the testicles; one of the arm, a male; three of the leg, one male and two females; and one of the breasts, a woman who was at the time suckling her baby, and whose milk I examined, but found no filariae in it. In these six latter cases examination of the blood gave negative results. At Lifuka, one case of elephantiasis of the arm, with no filariae in the blood, and one of the leg, with filariae present, both men, were examined.

A disease of the eyes, the etiology of which still seems to be a moot point, is extremely common in the Friendly Islands, namely, pterygium. It appears to have no relation to filariasis.

As will be seen from Table I the percentage of natives harbouring filariae in their blood differs considerably in the two sexes, and in the different islands. Two causes evidently account for these facts—namely, the conformation of the islands, and the habits of the natives. The Tonga Islands are for the most part flat; of the four islands named, Vavaū is the only one that has any pretensions to a hilly structure. Consequently, there are no running streams, and the natives are dependent for their drinking water upon wells dug in the coral limestone to collect the rain; the chiefs, however, and the higher classes of natives possess covered iron tanks for this

purpose. The island of Nomuka, where over 40 per cent. of the male population are affected with filariasis, possesses a very large salt water lake in its centre, besides many smaller fresh water lakes, and is, consequently, simply infested with mosquitos.³ It is certain that the majority of the inhabitants use the water from these lakes for drinking purposes. As regards the habits of the natives the prevailing custom of kava drinking is undoubtedly responsible for the spread of filariasis. It is a custom which is limited to a great extent to the men only, and this accounts for the smaller percentage of women affected with the disease. The chiefs, who live in a better style than the lower classes, and whose supply of water is from a purer source, though great kava drinkers, very rarely suffer from filarial diseases. They seldom drink water, except in the form of kava; otherwise they drink the milk of the cocoanut. One of the highest chiefs in the kingdom informed me that the only instance of elephantiasis occurring amongst the chieftain class that he knew of, was that of a chieftainess, who was in the habit of associating with her inferiors, a great dereliction of dignity, and so contracted the disease. But amongst the lower classes those who indulge greatly in kava drinking are especially liable to filarial disease. Undoubtedly this is due to the impure source of the water with which the infusion of the kava root (*Piper methysticum*) is made. The method of straining the infusion through a mass of "fau," the shavings of the bark of the cotton tree (a species of *Hibiscus*), must to a small extent act as a prophylactic measure, otherwise we might expect to find even a higher proportion of the natives affected with filariasis. It is a striking fact that the large majority of the natives in whose blood filariae were found were great kava drinkers.

We now come to the question—assuming that the filaria of the Friendly Islands is identical with *F. nocturna*—What are the causes which have so altered its habits that it no longer exhibits its usual periodicity? I cannot do better than quote a passage from Mariner's classic account of the "Tonga Islands,"⁴ written at the beginning of the century, an account, however, which still is accurate in these modern days, as I know from personal experience. The natives "employ themselves in conversation, not only at any time during the day, but also at night. If one wakes, and is not disposed to go to sleep again, he wakes his neighbour to have some talk. By-and-by, perhaps, they are all roused, and join in the conversation. It sometimes happens that the chief has ordered his cooks in the evening to bake a pig or some fish, and bring it hot in the middle of the night with some yams. In this case the torches are lighted, and they all get up to eat their share, after which they retire to their mats; the torches are put out, some go to sleep, and others perhaps talk till day-light." Here we have all the conditions necessary for the complete breaking up of filarial periodicity, for we know "that if sleep is indulged in for short times and at short intervals, and this habit kept up for several days, filarial periodicity becomes completely broken up, and is no longer maintained—that, in fact, filarial embryos, under such circumstances, are constantly present in the circulation."⁵ It would be interesting to see if filarial periodicity could be established in a native of Tonga, by causing him to sleep regularly during the night, and not at all in the day-time. The result of such an experiment would go far either to confirm or refute the theory that the filaria of the Tonga islands is identical with *F. nocturna*.

It is to be regretted that the ship did not visit either Samoa or the island of Rotumah, both of which localities are said to be hot-beds of elephantiasis to a far greater extent than exists either in Fiji or Tonga. I would draw the attention of medical officers who may have the opportunity of visiting them, to these places, more especially to Rotumah, where I think that a larger percentage of the inhabitants will be found to be affected with filariasis than possibly in any other locality in the South Seas.

³ It is an interesting question whether the name of this island is not derived from the native word "Nainu," meaning a "mosquito."

⁴ Vol. ii, chap. xxiii, p. 345.

⁵ Davidson, *Hygiene and Disease of Warm Climates*, p. 755.

MR. C. PENRUDDOCKE, M.R.C.S., L.R.C.P.E., Public Vaccinator for the Stapleford District of the Wilton Union, has been awarded the grant for efficient vaccination.