group of laryngeal muscles, and that these fibres appear to bear a fixed relationship to each other throughout their course, the abductors being situated on the inner side of the nerve, or that next to the trachea, while the adductors are on the outer side.

7. That it is possible to so accurately separate these two sets of fibres in the nerve trunk that excitation of either of them evokes contraction of the abductor or adductor muscles, as the case may be, without evoking any contraction whatever in the muscle or muscles of opposite function.

8. That the bundle of nerve fibres concerned with one function may be divided without injury to that concerned with the opposite function, and that such division is followed by atrophy and degeneration of the muscles related to that function without any such changes being detected in the muscles related to the opposite function.

These results prove Mackenzie's theory of superficial and circumferential arrangement of the abductor fibres in the recurrent laryngeal nerve to be erroneous. As regards the different effects observed in the young and adult dog, possibly the reason why the abductor influence is in the ascendancy in the young animal is because the power of phonation is still imperfectly developed, and with it both the muscle and nerve fibres subserving this function are also imperfectly developed, while the function of respiration is from the beginning fully developed, and with it the muscle and nerve fibres connected with that function. That the reverse should be the case in the adult animal may well be due to the fact that phonation is perfectly developed, while respiration has become so automatic that very feeble stimuli are necessary to keep it going.

ACUTE LEUCOCYTOSIS PRODUCED BY BACTERIAL PRODUCTS.

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THE observations of Römer and others have of late attracted special attention to the changes in the blood during infective processes. Römer¹ experimented on rabbits, while Canon,² Botkin,³ Neusser,⁴ and Tschistowitsch⁵ studied the phenomena as they occur in hospital patients.

Broadly speaking, these investigations show that after the injection—intravenous or subcutaneous—of bacterial products or extracts the number of leucocytes in the blood is greatly increased, and the same also occurs in the acute infective diseases. That leucocytosis is a common phenomenon in acute fevers is an old-established fact; but this question has recently become more important on account of its bearing on phagocytosis and "chemotaxis."

Some few months ago Mr. Hankin and I began some experiments with a view to studying the leucocytosis and fever produced by intravenous and subcutaneous injections of sterilised or filtered cultures, and in January we read a short communication before the Cambridge Philosophical Society on the "Fever produced by Intravenous Injections of Sterilised Cultures of *Vibrio Metchnikovi*." We showed that after injecting small quantities into the ear vein of a rabbit, as Gamaleia pointed out, a considerable rise of temperature occurs, the maximum (40.5° to 41.0° C.) being generally reached after two or three hours. Subsequently the temperature gradually falls again, and after eight to ten hours as a rule has come down to normal. Examining the blood hourly, we showed that at first, during the rapid rise of the temperature, there is a marked diminution of leucocytes, which persists until the pyrexia has passed its climax, but that about four to six hours after the intravenous injection the number of leucocytes is greatly, and at times almost enormously, increased. This leucocytosis reaches its height at about the ninth hour, but persists, though in a lesser degree, for forty-eight to seventy-two hours, and at times even

longer. We represented these phenomena by the following diagram:—

Fig. 1.—Temperature and leucocytosis curves.

These observations agree with those of Römer, who, also working on rabbits, obtained a diminution stage followed by a great increase of leucocytes.

Besides the products of *vibrio Metchnikovi*, filtered yeast and pyocyanus cultures have been employed with uniformly the same result. The immediate effect of the intravenous injection is fever, the nature of which may be best seen from the three appended charts:—

A.

B.

C.

Fig. 2.—A, 4 c.c. of sterilised pyocyanus culture into ear vein at 11.0 A.M. B, 1 c.c. of sterilised *vibrio Metchnikovi* culture into ear vein at 12. C, 4 c.c. of filtered yeast culture into ear vein at 11.0 A.M. The leucocytes behaved in the same manner as after injection.

¹ *Berliner klin. Wochenschr.*, 1891, No. 36; *Virchow's Archiv*, 1892, No. 128, 1.

² *Deutsch. med. Wochenschr.*, 1892, No. 10.

³ *ibid.*, 1892, No. 15.

⁴ *Wiener med. Presse*, 1892, Nos. 3, 4, and 5.

⁵ *Berliner klin. Wochenschr.*, 1891, No. 34.

tions of the products of the vibrio, as will be best recognised from the following notes of a typical experiment:—

January 29th, 1892, 11 A.M. Rabbit; 4 c.c. of sterilised pyocyanus culture injected intravenously (1 : 506).
 11.45 A.M. Decrease of leucocytes (1 : 937).
 12.15 P.M. Further decrease (1 : 1,243).
 12.45 P.M. Still further decrease (1 : 1,935).
 1.30 P.M. No change (1 : 2,006).
 2 P.M. Leucocytes beginning to increase (1 : 876).
 3.35 P.M. Decided increase (1 : 312).
 4.30 P.M. Increase well marked (1 : 305).
 6 P.M. Enormous increase (1 : 124).
 6.45 P.M. " " (1 : 137).
 January 30th, 11 A.M. Still very marked leucocytosis (1 : 259).
 The figures in brackets indicate the proportion of white and red corpuscles.

At the same time, following a suggestion by Mr. Hankin, I studied the nature of the leucocytes participating in this increase, directing my special attention to the eosinophile corpuscles. If it be allowed that "chemotaxis" and phagocytosis are the most important processes in the acquisition of immunity, a leucocytosis caused by the absorption by the blood of bacterial products must be of great value by supplying an increased number of potential, if not actual, phagocytes. Now, among the leucocytes there is one form, the eosinophile, which is never phagocytic, and another, the ordinary small lymphocyte, is but rarely so;⁶ and if the leucocytosis should affect these cells in special very little would be gained from an increase of leucocytes as far as phagocytosis is concerned.

Briefly speaking, in the blood we distinguish between basophile, eosinophile, and neutrophile corpuscles, according to whether their protoplasmic granulations stain with basic, acid, or neutral dyes. The case in the rabbit is slightly complicated by the fact that many cells are amphophile; that is their granules stain with either the acid eosin, or the basic methyl blue. I found, however, that on using a modification of Ehrlich's eosin method, these corpuscles react as eosinophile only. The method is as follows: a coverglass film of blood is prepared in the usual manner and dried, and then placed in a warm alcoholic solution of eosin for some time. When thoroughly stained it is washed under the tap and rapidly heated on a copper plate and finally counterstained with aqueous methyl blue. By this means all the amphophile (and eosinophile) cells react and stain alike, and can be easily distinguished from the lymphocytes and other elements. This method has this other advantage, that it also fixes the eosinophile granules that have been discharged from the leucocyte and are free in the plasma or taken up by other cells.

I have convinced myself, after a most extensive examination of the changes in the frog and rabbit, that all the leucocytes which react as eosinophile according to this method are never phagocytic. Now, in the rabbit it is especially these latter which are increased during the acute leucocytosis produced by bacterial substances. In some cases besides the eosinophile cells and lymphocytes extremely few of the other cell elements are seen, but always the eosinophile cells are increased in greater proportion than any of the other leucocytes.

The eosinophile cells frequently, if not generally, occur in clusters of from 4 to 12, and are of varying size. Many are apparently in the process of discharging their eosinophile granules, while others have, so to speak, exploded, the granules lying interspersed among the red corpuscles. That this discharge of the granules is not due to mechanical rough treatment can be shown by watching the eosinophile cells of the frog on a warm stage; and on using the above method of staining it is easily seen that phagocytes (especially in the frog) not infrequently take up some of the discharged granules. It is therefore permissible to regard these cells, as Ehrlich does, as secretory, and to assume that they constantly discharge their granules into the blood.⁷

To obtain an approximately accurate estimate of the absolute and relative numbers of the various leucocytes the hæmocytometer of Thoma-Zeiss was employed, the blood being

diluted with Toison's solution,⁸ and also Canon's method⁹ of counting the leucocytes in a large number of microscopic fields, and thence calculating their percentages. By examining in each instance hourly six to ten coverglasses, errors of observation were obviated as far as possible with such methods. These enumerations have shown: (1) that in rabbits after the injections of bacterial products it is especially the eosinophile cells which are increased, (2) that often the eosinophile cells are more numerous than all the other classes of leucocytes taken collectively, and (3) that almost always the eosinophile cells are more numerous than any other class of leucocytes taken by itself, and (4) that the transitional and neutrophile corpuscles are increased least, and often not at all.

In this respect then we notice a great difference from Botkin's¹⁰ and Tschitowitsch's¹¹ observations in man. They found that in the acute tuberculin leucocytosis all the various forms of leucocytes are increased, but especially the neutrophile, and where a considerable proliferation of eosinophile cells seems to have taken place, this, according to Botkin, is not dependent on an individual injection of tuberculin, but is rather the sum total of all the separate injections and reactions. Canon,¹² on the other hand, found an actual diminution of the eosinophile cells of the human blood in acute infective diseases. Neusser,¹³ however, established in man also an increase of the eosinophile cells as the effect of various toxins.

The bearing on phagocytosis of the above observations is evident, especially if it be considered that the same phenomena occur in immunised animals (for example, rabbits protected against the bacillus pyocyanus). It would, however, lead us too far to discuss this point here.

According to Botkin the leucocytosis, in the case of tuberculin injections, is independent of the fever. This is quite true to a certain degree, as in some instances, while experimenting on animals, leucocytosis may be observed without a rise of temperature. But it is a significant fact that the stronger the febrile reaction has been, the more marked is the leucocytosis, and, generally speaking, the acute leucocytosis induced by bacterial products is accompanied by febrile reactions. But, so far as rabbits are concerned, it cannot be said that the temperature and leucocytosis curves rise and fall together, as, according to v. Limbeck,¹⁴ is the case in human febrile inflammatory processes (for example, pneumonia, erysipelas, pleurisy, peritonitis, purulent meningitis). As a matter of fact, for our animals in which a passing pyrexia was produced almost the reverse is true. The climax of the fever is followed by a rise in the number of leucocytes, and this would seem to point to extensive general changes in the tissues of the bodies. And this brings us to the question—where do the eosinophile cells come from? I shall abstain from entering fully into this matter, leaving it for future discussion, all the more as our knowledge regarding the origin of leucocytes is still very imperfect and my own observations yet incomplete.

Römer contends that the bacterial substances exercise a formative stimulus (*formativen Reiz*) on the white cells in the blood and especially within the veins, where the leucocytes multiply after the type of an amitosis (fission). He bases his views chiefly on the facts that (1) the leucocytosis is but slight in the arterial blood though well marked in the venous; and (2) that he has frequently observed leucocytes in the process of division. With regard to the first point, I have constantly noticed an increase of leucocytes as great in the arteries as in the veins, and there also found the eosinophile cells arranged in groups and clusters.

Unfortunately, Römer did not differentiate the various forms of leucocytes by means of staining reactions, so that it is impossible to gather from his account whether his description applies to the eosinophile cells or to the other elements. In the blood I have never observed eosinophile cells in a process of division, whether by means of fission or mitosis. In the connective tissue of the frog and in the marrow of bones (guinea-pig) mitotic division of the eosinophile cells can be occasionally observed, but, like H. F. Müller, I

⁶ Cf. Metschnikoff's *Leçons sur la Pathologie Comparée de l'Inflammation*, p. 136; and W. B. Hardy's suggestive paper on the Blood Corpuscles of the Crustacea, *Journal of Physiology*, xiii, 1 and 2, p. 183.

⁷ Cf. also Hardy, *Op. cit.*, page 176.

⁸ Cf. *Mikroskopische Technik*, von C. Friedländer, 1889, page 150.

⁹ *Loc. cit.*

¹⁰ *Loc. cit.*

¹¹ *Loc. cit.*

¹² *Loc. cit.*

¹³ *Loc. cit.*

¹⁴ *Zeitschrift für Heilkunde*, xvi.

have never seen this phenomenon in the circulating blood.¹⁵ There is no doubt that the eosinophile cells normally are not formed to any extent in the spleen, for even after splenectomy a rabbit reacts in identically the same manner as an intact animal; the febrile reactions and the leucocytosis are the same.

According to Ehrlich¹⁶ eosinophile cells are copiously found in the bone marrow of rabbits, while the spleen and mesenteric glands contain but few. However, on killing a rabbit during the climax of the leucocytosis, or allowing it to die after an infection with anthrax, these organs are often crowded with eosinophile cells. The curdy pus of rabbits also contains great numbers of them.

It seems that these characteristic cells are developed outside the circulating blood. In 1879 Ehrlich suggested that, as far as the frog is concerned, these cells are derived from the fixed connective tissue cells. It is remarkable to watch the number of eosinophile cells which make their appearance on inoculating a "cold" frog with anthrax under the skin of the thigh, yet the number of these cells in the blood remains unaltered. To explain this by "chemotaxis" is unsatisfactory and inadequate, for the same occurs on using the amputated leg, having previously applied a ligature for two or more hours. These observations on the frog tend to show that these cells are produced by means of a formative irritation, and not attracted into or from the circulating blood by some mysterious power. How the matter stands in the case of man and warm-blooded animals it is difficult to state as yet. Conclusions derived from the leucocytes and wandering cells of cold-blooded animals cannot at once be applied to the same structures in higher animals.¹⁷ The homology of the various cellular elements of the blood and connective tissue has yet to be established. It is, however, highly suggestive that Neusser and others found an increase of the eosinophile cells in a certain number of chronic skin diseases and several of the exanthemata, not only in the blood but also in the skin itself.

The systematic examination of the blood in clinical practice, according to Ehrlich's classical methods, has hitherto been too much neglected in England, and it is desirable, on account of the special attention which modern theories have drawn to the leucocytes, that clinically also we should become familiar with the changes brought about in the blood corpuscles by infective and other processes.

MEMORANDA:

MEDICAL, SURGICAL, OBSTETRICAL, THERAPEUTICAL, PATHOLOGICAL, ETC.

ULCERATIVE STOMATITIS.

As is well known, this affection is styled in some textbooks "ulcerative" or "diphtheritic" stomatitis, and is regarded by some as being of a diphtheritic nature, and by others as having no etiological resemblance to true diphtheria. The details of the following cases, I think, seem to favour strongly the theory of the former.

CASE I.—G. S., female, aged 28, after some degree of feverishness and *malaise* for about four days, complained of sore throat. On examination diphtherial patches were observable on both tonsils. As the patches cleared the gums and cheeks became affected with typical "ulcerative stomatitis."

CASE II.—About the same time F. C., female, aged 19, living in the same house, complained of sore throat, and was found on examination to have well-marked and extensive diphtherial patches on the right tonsil and also slightly on the left. There were no signs then of stomatitis. She only felt slight soreness of the gums as the throat symptoms cleared up.

CASE III.—A child, aged 2 years, female, in the same family, who was at this time apparently quite well, was sent away to another district some miles distant. Before going her throat

and mouth were examined and found quite healthy. Five days after her departure she was suddenly taken ill, found to be very feverish, and was noticed on the following day to be suffering from "ulcerative stomatitis;" but no patches of any kind were discoverable about the fauces. Her throat remained clear throughout her illness, which lasted about ten days.

The week preceding the onset of these cases another adult female in the same house was suffering from slight sore throat, which was diagnosed and treated as a relaxed sore throat from chill.

The main points of interest were that in Case I there was diphtheria with ulcerative stomatitis; in Case II diphtheria with no recognisable stomatitis; and in Case III ulcerative stomatitis with no recognisable patches of diphtheria; this case also showing the specific nature of the ulcerative stomatitis by the definite period of incubation observed after the child's removal to another district.

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TREATMENT OF DIPHTHERITIC PARALYSIS.

WHILE reading the record of cases of paralysis of the diaphragm by Professor Suckling in the BRITISH MEDICAL JOURNAL of May 28th, I was surprised at the extreme misfortune which seems to have attended the cases of diphtheritic paralysis, all of them (3) being fatal. This mortality is, I believe, much greater than what generally occurs; in fact, it was the opinion of the late Professor Ross that only a small percentage of such cases was fatal, and I believe this is the generally accepted opinion. A case which bears this out occurred at the Clinical Hospital, Manchester, lately, the patient, a boy aged 5 years, illustrating what might be called a typical case. After some time, diaphragmatic paralysis supervened, with orthopnoea and pulse irregular, both in force and frequency. He was treated with careful feeding and hypodermic injections of liq. strych. $\frac{m}{j}$ quat. die, under which treatment the paralysis of the diaphragm disappeared in about a week, the injections being continued thrice a day for two weeks longer, the duration of illness altogether being about six weeks.

If one may judge from Professor Suckling's cases and several cases of diphtheritic paralysis—not diaphragmatic—which I have seen treated by oral administration, there certainly seems a wide difference between the results, the hypodermic method being much the more satisfactory, being much quicker and more reliable. This also coincides with the experience of English and Continental observers. The possibility of abscess formation should not be a bar to its use; for during the whole of the above and of a fairly extensive experience in other cases, I have not yet met with a single case where an abscess followed the insertion of a clean needle.

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HEMORRHAGE FOLLOWING TONSILLOTOMY IN A BLEEDER.

HAVING read Mr. Lane's case in the BRITISH MEDICAL JOURNAL of April 30th, I thought the notes of a case which nearly ended fatally might be of interest. Two years and a half ago, when house-surgeon at the South Devon Hospital, Plymouth, I removed the tonsils of one of the nurses, aged 21, with a bistoury, not knowing at the time that she had a hæmorrhagic tendency. I did not notice any extraordinary bleeding at the operation, but two hours later was sent for, as the bleeding was still going on, and a large quantity of blood had been expectorated and vomited.

For the next two hours, with the help of Mr. R. H. Lucy, assistant surgeon to the hospital, who happened to come in, various means of arresting bleeding were tried. These included pressure with iced sponges and pads of lint on the bleeding surfaces, with counterpressure externally over the tonsillar region, various styptics locally and ergotone internally. Still the bleeding continued, and about four pints of blood were lost. Syncope supervened, the pulse became almost imperceptible, jactitations occurred, and we feared death would take place. We then injected two or three pints of warm saline solution into the rectum. This was all absorbed, the pulse rapidly improved, and luckily at this time,

¹⁵ H. F. Müller, Ueber Mitosen an eosinophilen Zellen, *Archiv für experiment. Pathol.*, xxix, 3 and 4, p. 221; also Dekhuijzen, Ueber Mitosen in freilieg. Bindegewebe gelegenen Leukocyten, *Anat. Anzeiger*, vi, 8, p. 220.

¹⁶ *Berlin Physiol. Soc.*, Jan. 17th and May 16th, 1879.

¹⁷ Cf. Hardy's paper on this point.