Thomas Houston

President of the Ulster Medical Society 1920–21

Presidential Opening Address
Ulster Medical Society
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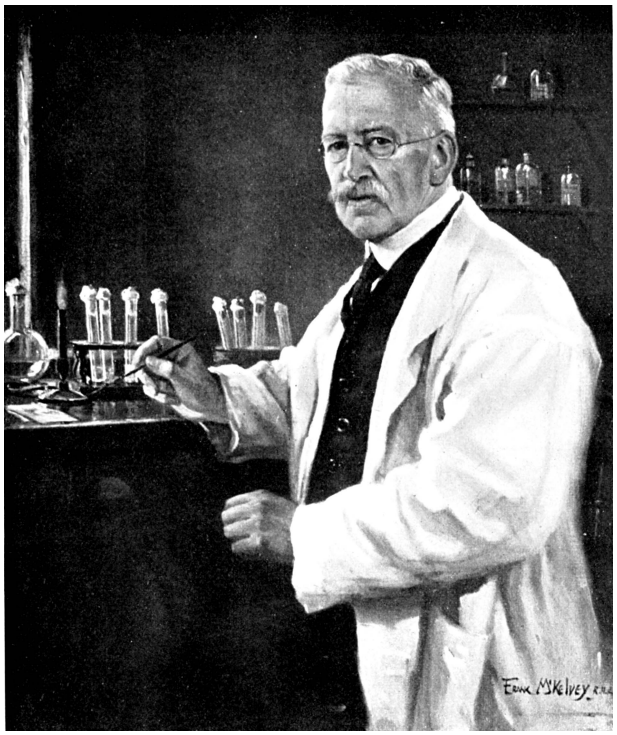
BEHAVIOUR OF LEUCOCYTES
IN INFECTIONS AND IMMUNITY.

Ladies and Gentlemen, My first duty as President is to thank you, the Fellows and Members, for the great honour you have conferred upon me by asking me to preside over the destinies of the Ulster Medical Society for the coming year. When I think of the long list of distinguished men who occupied this chair I feel very conscious of my shortcomings, and I can only say that I will endeavour to follow in their steps and do what in me lies to further the interests of our Society.

My second duty is one of the saddest and most trying that any President of this Society has ever been called upon to perform. Since January of the present year the Last Post has sounded for an unusually large number of our members: we have lost by death six of our Fellows, including three ex-Presidents of our Society. All of these men were intimate personal friends of my own, and of many of you who are here to-night. Personally I feel that my world is much the poorer for their loss, and I know that this Society has suffered an almost overwhelming calamity.

DR. GEORGE ADAM HICKS, F.R.C.S.,Ed., died at his residence in College Gardens on January 24th, 1920. His death was due to a streptococcic infection contracted in the discharge of his duty. Dr. Hicks was a native of Sligo, but was educated at Queen's College, and passed his professional life in Belfast. He graduated M.B., B.Ch., B.A.O. in 1897, obtained the M.D. in 1904, and the F.R.C.S.,Ed., in 1912. On the retirement of Dr. J. St. Clair Boyd from the Samaritan Hospital for Women he was elected surgeon in his stead. He now specialised in gynaecology and obstetrics, and rapidly obtained a very large consulting practice in this department of medical work. He was universally respected by his professional colleagues, and was greatly beloved by his patients. He was unremitting in his attention to his work, and few men have lived a more arduous and strenuous life. He took a great interest in this Society and we were frequently indebted to him for



communications of great interest and ability. He was a man of deep religious convictions and genuine charity.

DR. F. C. SMYTH died in the Royal Victoria Hospital on the night of June 15th, from a fracture of the base of the skull, the result of a motor accident which occurred after he paid an emergency visit late at night. Dr. Smyth was only 41 years of age. He graduated in the Royal University of Ireland in 1903 and took the M.D. in 1908. He was assistant physician and secretary of the Staff to the Ulster Hospital for Children and Women; medical officer to two sections of the Royal Irish Constabulary, and had a large general practice in Belfast. He was a great favourite with his colleagues in the profession, and was held in much affection and esteem by his patients. He was an all-round man, played a good game at golf, took a great interest in the meetings of this Society, and in general professional matters.

SIR ALEXANDER DEMPSEY, M.D., died at his residence, Coldagh, Somerton Road, Belfast, after a short illness, on July 18th, 1920. He was born at Coldagh, Ballymoney, Co. Antrim, in 1852, and obtained his collegiate education at Queen's College, Galway, and the Roman Catholic University Medical

School, Dublin. He obtained the M.D. in the old Queen's University in 1874. He was a man of broad general interests and high professional attainments. Along with the late Dr. John Moore and the late Dr. William M'Keown he established the North of Ireland Branch of the British Medical Association, in which he always took a keen interest; for many years he acted as its honorary Secretary and Treasurer, and subsequently he was elected its President. When the Association met in Belfast in 1884 he was one of the honorary secretaries. He was President of this Society in 1890-1891, and one of the Trustees of the Medical Institute. He made many valuable contributions to our Society, and was a constant attender at our meeting's.

Sir Alexander Dempsey was much associated with the public life of this city, he was appointed a Justice of the Peace in 1860; for many years he was a member of the joint board of the Belfast and County Antrim Asylum, and of the Visiting Committee of the Belfast Prison. He was elected a member of the governing body of the University College, Dublin, and nominated at its inception a member of the National University Senate, Two years ago he became a senator of the Queen's University of Belfast.

He was gynaecologist to the Mater Infirmorum Hospital, Belfast, and took a deep interest in the welfare of this Hospital. He had a large general practice, and frequently was called upon as a consultant. He, on several occasions, acted as local examiner in obstetrics and gynaecology in the Queen's University, and as extern examiner in the National University of Dublin. In 1911 he received the honour of knighthood.

Sir Alexander Dempsey was a great favourite among his professional brethren, and with the public generally. He was a man of broad views and sympathies, and had a logical and astute mind.

MR. ROBERT CAMPBELL, M.B., F.R.C.S., Eng., died in his 55th year at his residence, 22, College Gardens, Belfast, on September 6th. For several years he had suffered from Bright's Disease, and his death was the result of uraemia.

Robert Campbell was the son of the Rev. Robert Campbell of Templepatrick. He had a most distinguished College career in Arts and Medicine, and in his final examination for the M.B. degree he obtained first place. He was appointed demonstrator of anatomy in Queen's College, Belfast, and was subsequently resident to the Chester Infirmary. In 1896 he obtained the F.R.C.S., Eng., and settled in Belfast as a surgeon. He was surgeon to the Royal Victoria Hospital and to the Queen Street Hospital for Sick Children. His obituary notice in the British Medical Journal is written with such a keen insight into his character and professional attainments that it deserves to be handed down in the records of this Society, of which he was President in 1918-1919:—

"All his work was distinguished by great skill, meticulous care, originality, and by what might be termed a restrained and discriminating boldness. He was among the first to use indiarubber gloves, and early introduced them into the Belfast School. As early as 1898 he operated for perforating typhoid ulcer. In 1910 he distinguished clearly between acute appendicitis and acute appendicular obstruction, and put his proofs so vividly before the profession that he was undoubtedly the first to insist on the difference in the pathology, symptoms, course, and dangers. His operations for congenital hernia in infants were numbered by the hundred; and while high surgical authority was laying down rules as to age and other limitations, he was performing them in a steady stream, regardless of such restrictions and with convincing success. His work and operations on thyroidectomy were also characterised by the same fulness, completeness, and success. Mr. Campbell was also surgeon to the Ulster Volunteer Force Hospital, and gave his skill and experience ungrudgingly to the wounded soldiers and pensioners. He was president of the Ulster Medical Society in 1916-1917, and of the Ulster Branch of the British Medical Association in 1918-1919, and his opening address on both occasions was marked by wide experience, a penetrating and scientific intellect, and philosophic breadth. During the latter years the strain of a large consultant and operative practice, and perhaps the insidious development of his disease, kept him from publishing his views and results with the fulness that their importance demanded. In his younger days, also, his teaching of surgery was described as perfect; latterly he evidently felt the necessity to economise his strength, but still at times spoke with that clearness, brevity and discernment that said what was necessary and omitted what was unnecessary. At times he was the most silent of men, but to the last his personal friends enjoyed the keen perception, the silent humour, the straightforwardness, and yet the broad charity of his conversation.

"Mr. Campbell was a leader among the band of surgeons trained in anatomy under the late Professor Redfern, that revolutionized surgery in the Belfast school. He had the rare combination of a large brain, practical common sense, unerring instinct, and well-trained hands. His friends will miss his true devotion; and the profession and public, for whom he worked as long as strength lasted, a most trustworthy,

skilled, and high-principled servant."

SIR JOHN BYERS died on September 20th, in his 67th year from cerebral haemorrhage. His death followed closely on that of his friend, Mr. Robert Campbell; in fact, while returning home from the Royal Victoria Hospital where he had proposed a vote of sympathy with the friends of Mr. Robert Campbell at the Meeting of the Board of Management he was taken from his motor unconscious and never rallied.

Sir John was born at Shanghai in 1853, and was the son of the Rev. John Byers, a China missionary. He had a most distinguished academic career at Queen's College, Belfast. Both at the B.A. and M.A. examination he was gold medalist, and first on the honours list. At the M.D., M.Ch. (R.U.I.) he again took high honours. He began practice in Belfast and was appointed physician to the Hospital for Sick Children. In 1893 he was appointed professor of Midwifery in Queen's College, Belfast. He also acted as examiner in Obstetric Medicine in the Royal University of Ireland. In 1909 he was appointed to the Chair of Midwifery, Gynaecology and Diseases of Children at the Queen's University, which post he still held at the time of his death. He took a great interest in public affairs relating to the health and welfare of the community. He was a ready and able speaker, and the meetings of this Society have often been invigorated by his stimulating oratory. He was President of this Society in 1893 and 1894.

He took a great and practical interest in child welfare, and in an introductory address to the students of the London School of Medicine for Women in 1906 he foreshadowed the important part that women were soon destined to play in the solution of public health questions. His wife, Lady Byers, was, two years later, instrumental in establishing the first babies' club in Belfast.

Sir John made a "hobby" of the study of the folklore and provincialisms of Ulster. His contributions to the Belfast Literary Society and the Natural History and Philosophical Society in Belfast were always interesting and instructive.

Sir John received the honour of knighthood in 1906. He was a man of high ideals, of strong likes and dislikes, of resistless energy, and of stimulating personality. He had the courage of his convictions, and was not afraid to say what he thought.

DR. B. H. STEEDE, died on September 30th, from the pressure effects of a mediastinal tumour. During his illness he obtained very remarkable temporary benefit from Radium treatment, but in the end the symptoms returned and he died in a Dublin Hospital. He was qualified in 1893 and made a special study of pulmonary tuberculosis. He had medical charge of the Rostrevor Sanatorium for many years. He became a Fellow of this Society in 1906, and his knowledge of diseases of the chest was extensive and thorough. It is to be regretted that his widow and family are left without proper means of support. An effort is being made by his professional friends on their behalf, and we hope that the members of this Society will subscribe as generously as possible towards this deserving object.

The subject which I have chosen to direct your attention to on this occasion is that of the behaviour of the leucocytes in infection and immunity. Historically this subject forms perhaps the most instructive and fascinating chapters of the vast record of the scientific work that has been done on immunity. I well remember my first introduction to this subject when, many years ago, I listened to the Professor of Surgery's lectures on inflammation. He described the slowing of the blood stream, the exudation of the plasma, the diapedesis of the leucocytes, the phagocytosis of the invading organisms. Here was a veritable fairytale of science. Surely this was a somewhat fanciful picture to invest with a tinge of romance the dolor, calor, rubor, tumor of the inflammatory process. But, as afterwards I devoted much time to the study of these leucocytes and to their behaviour in infective processes, I have come to the conclusion that the Professor's word picture was far from fanciful, and that not one-half of the wonders of the white cells of the blood had then been told me.

The white cells of the blood are divided into different classes which are distinct in their origin, properties and form. The merit of this differentiation of the white cells into groups is due to the genius of Ehrlich, and especially to the staining methods which he introduced. Since his work on this subject very little has been added to his classification and theories of the origin of the different groups, so that the description given by him is now accepted in its essential details by all students of haematology. An interesting story is told of how Ehrlich mystified the scientific workers of Europe. He described in detail the preparation of what is now called "Ehrlich's triple stain," and showed how by the use of this stain the most beautiful demonstration of the granules of the polynuclear leucocytes could be obtained. However, no pathologist was able to reproduce his results, and it was asserted that Ehrlich was holding back some essential detail. He was finally asked to explain the mystery, and it transpired that the universal laboratory custom was to filter all stains before use,

whereas the triple stain loses its properties if it is filtered. Ehrlich's description did not state that the stain should be filtered.

The leucocytes of the blood have been divided by Ehrlich into mononuclears and polynuclears. The mononuclears are again divided into two classes – the small mononuclears or lymphocytes, and the large mononuclears. The lymphocytes are in the main derived from the lymphatic glands and the lymphatic tissues throughout the body. These cells form about 23% of the total leucocytes of the blood in normal conditions. They are practically non-amorboid and do not act as phagocytes. According to Ehrlich's view the large mononuclears are totally different cells and are believed by him to arise from the bone marrow. They form 2–6% of the total number of leucocytes. They are phagocytic but are more active in the englobement of cellular elements such as dying red cells and tissue debris than in the phagocytosis of bacteria. Both these mononuclears cells have non-granular protoplasm. It was at first thought that the lymphocytes were the young cells of the blood and that the other forms were derived from them. This view is not now tenable as the different cells have different origins in the haemopoietic system, and one class does not develop into another.

The blood contains a very large proportion of the polynuclear cells, 60–70%. This term is in reality a misnomer, as these cells have only one nucleus, divided into lobes, connected by fine strands of nuclear substance. They are very actively amorboid and phagocytic, and contain granules which are well demonstrated by the use of Ehrlich's triple stain. These granules are sometimes called acido-phile on account of their greater affinity for acid than for basic stains. Ehrlich has styled these granules neutro-phile, which is perhaps the most correct term. These cells are derived from the bone marrow and are the offspring of the myelocytes, which are the single nucleated granular cells of the marrow. In the course of development these myelocytes divide, become amorboid, and their nucleus takes on the twisted polynuclear form, no doubt as an adaptation which facilitates their amorboid movements through the interstices of the tissues. This polynuclear cell has a truly wonderful power of amorboid motion. It cannot swim, but, given a scaffolding, it can find its way almost anywhere. One of the most beautiful demonstrations of their amorboid power is Sir Almroth Wright's method of showing how polymorpho-nuclear leucocytes will migrate from the clot and attach themselves to a glass surface. The method is as follows:– Little glass windows are made on a microscopic slide by means of heated paraffin brushed over little squares of paper adhering to the slide. When the paraffin has set the pieces of paper are detached, leaving a square window surrounded by paraffin. The windows are now filled with drops of blood, and the preparation put into the incubator for twenty minutes in a moist chamber. The blood clots are now exposed to the full blast of the tap, and the clot and red cells are thus washed away, but the leucocytes, when examined under the microscope, are found adhering to the glass in countless numbers. If the preparation be now fixed and stained with methylene blue, the leucocytes are seen on the glass in wonderful shapes, – bizarre elongations of the protoplasm and nuclear substance. Each leucocyte has been fixed in the abormoid contortion which it occupied before being subjected to the fixitive. The whole experiment is very simply and easily performed, and forms a most fascinating demonstration of the amorboid power of the polynuclear leucocyte. Wright first showed me this in the Laboratory at Etaples, and an Italian doctor from Rome was present at the time. These Italians know how to pay compliments. He said to Wright, "I have come all the way from Rome to France to learn of the medical work in this great war. It is sufficient reward to have seen this wonderful demonstration."

There also exists in the blood 2 to 4% of cells called eosinophile cells. Their form is similar to that of the polynuclear cells, but the nucleus is more regularly lobed and the protoplasm is literally stuffed full of coarse granules which stain well with eosine. They are derived from the eosinophile myelocytes of the bone marrow. They are amorboid but only slightly phagocytic, and this is probably due to the fact that they are so filled with large granules that there is little room for more particles.

The blood also contains a very small proportion – 5% – of cells called "mastzellen." They are similar to the eosinophiles except that their protoplasm contains large granules that stain strongly with basic stains, such as methylene blue. Although normally the origin of the different varieties of leucocytes is what has already been stated, yet in pathological conditions the role of the bone-marrow may be taken on by the spleen, liver or lymphatic tissue. This is called the myeloid transformation of the spleen and lymphatic tissues. In such conditions a large number of proliferating cells, having the same appearance and characters as the myelocytes of the bone-marrow, may be found in the spleen and lymphatic tissues. Delaet has recently shown, when doing experiments on the culture of tissues in vitro, that new formations

of polynuclear cells may occur through the influence of microbic toxines. It has been shown, for instance, that if a guinea pig is injected with typhoid vaccine that a large leucocytosis of polynuclears is produced, reaching its maximum in twenty-four hours. If a similar injection is given to a guinea pig and its spleen afterwards aseptically removed and submitted to a suitable culture medium in vitro, the pieces of spleen in the nutrient medium are found in two or three days to be covered with polymorpho-nuclear cells; while if the animal has not been injected before the splenectomy only a proliferation of the mononuclear and tissue elements is found.

The variations of the leucocytes, both in numbers and type, form, no doubt, a picture more or less characteristic of any and every disease, but the methods at our disposal for studying their infinite variations in number and type are defective and laborious, so that it is only in diseases with very striking leucocyte pictures that the enumeration of the leucocytes and their differential count forms a valuable asset in the diagnosis of disease. In such blood diseases as lymphatic or myeloid leukaemia the number of leucocytes and their differential count generally makes the diagnosis of the condition certain. The nature of these diseases which present such an enormous increase in the white cells of the blood still remains a mystery. We have not yet found any better theory of the causation of the leukaemias than the old view of Cohnheim, that such conditions could be best explained as malignant tumours of the leucocyte tissue, owing their peculiar features to the fact that the blood is a circulating and not a fixed tissue. Thus the leucocyte tissue, both in the bone-marrow and lymphatic tissues, as well as in the circulating blood itself, shows all the evidence of the abnormal tissue proliferation so characteristic of tumour formation.

The other possible view is that such diseases are infections of unknown origin. One or two observations that I have come across in the course of my work seem to favour the infective theory. For instance, I remember several years ago being asked to examine the blood of a case of Professor Lindsay, in the old Royal Hospital. The patient was suffering from a fairly typical attack of crupous pneumonia. The leucocytes were enormously increased in numbers, 200,000 per c.m., and of these leucocytes 90% were lymphocytes. I thought the case was one of lymphatic leukaemia complicated with pneumonia. Repeated examinations were made, but the lymphocytosis gradually disappeared, and the blood picture eventually returned to the normal. I also remember examining the blood of a case of severe sepsis under the care of Professor Sinclair. The patient had had his arm amputated at the shoulder joint, and was extremely ill. His blood showed a leucocytosis of about 150,000 per c.m., and the differential count showed a high percentage of myelocytes. This blood picture also gradually disappeared as the patient became convalescent.

These cases are very exceptional, though similar findings may be found recorded in the literature of the blood. They seem, however, to show that a definite or multiple infective process may, under certain conditions, produce a blood picture closely simulating either lympathic or myeloid leukaemia, and consequently we might argue that these two blood diseases may be the result of an infective process of unknown origin.

LEUCOCYTOSIS.

The production of an inflammatory exudate is a local leucocytosis, but at the same time the stimulation produced, by the microbic products, on the blood forming organs frequently causes an increase of the total number of leucocytes in the organism. This general leucocytosis, as it is called, presents many interesting features. Leucocytosis is not entirely the result of microbic poisons: nucleinate of soda, broth, foreign serum and certain vegetable poisons may all produce a marked increase in the number of the circulating leucocytes. A small dose of peptone injected intravenously will produce a leucocytosis which may last for one or two months. Colloidal substances produce a leucocytosis. The intravenous injection of foreign blood cells produces at first a hypoleucocytosis, which is soon followed by a hyperleucocytosis. The leucocytosis produced by the injection of organisms or foreign cells is much more marked in an animal that has been immunized to these substances. A slight leucocytosis also occurs when blood is effused into the tissues. The production of an increase of the circulating leucocytes seems frequently to have a good effect on the organisms, and may, in some measure, account for the good effects of what is called protein shock therapy, and the results sometimes obtained by non-specific immunization. However critical we may be of such methods, it must be admitted that such results are in keeping with the dominant part which the leucocytes undoubtedly play in the processes of immunity.

When microbic products find entrance into the organism the first effect is a leucoplenia, and the leucocytes take refuge in the internal organs. This is usually followed by a marked leucocytosis which

generally lasts in a more or less pronounced manner while the infection continues. In some rapidly fatal infections, however, the leucoplenia persists until death. The enumeration of the circulating leucocytes can only give us a very imperfect picture of their increased formation in septic conditions. Consider for a moment a large discharging abscess pouring forth pus. This pus may amount to ten ounces in the twenty-four hours. Each cubic millimetre will contain 5,000,000 pus cells or more: that is, a cubic centimetre will contain 5,000,000,000 cells, so that ten ounces might well contain 1,500 billion of pus cells. At the same time, the general leucocytosis in the blood will be increased four or fivefold. This gives us some idea of the enormous increase in the formation of white cells in such septic conditions.

In the main we must consider an inflammatory leucocytosis as a salutary phenomenon; the increased formation is a defensive reaction of the organism. However, it will be at once seen that any prognostic indication from a marked leucocytosis must be weighed with extreme caution. In acute pneumonia an absence of leucocytosis is an exceedingly grave sign, but a marked leucocytosis does not necessarily signify a favourable issue of the struggle. When an inflammatory process abates, the leucocytosis diminishes; when a fresh exacerbation occurs the leucocytes again increase. If an empyema or abscess forms, the leucocytes will increase in numbers. All these possible factors must be duly weighed before a favourable prognosis can be founded on a marked leucocytosis.

In different infections we obtain very different leucocyte pictures.

In the majority of acute infections the polynuclear are the elements that are mainly increased. Their numbers remain augmented during the active period of the disease, but as the process subsides they decrease, while at this stage the mononuclears show at least a relative increase. The conception seems to be that the mononuclears begin to appear as soon as the active process is at an end, and their function seems to be the restitution of the tissues and the elimination of the debris.

Polynuclear leucocytosis is marked in pneumonia, diphtheria, appendicitis, and in staphylococcic and streptococcic infections, and with all micro-organisms that tend to produce suppuration. Normally the leucocytes number about 6,000 per c.m., while in infection their number rises to 20,000 or 30,000 or even more. At the same time the proportion of polynuclears also increases from 65 to 90% or more. This polynuclear leucocytosis of acute infection has often been made use of in diagnosis. In the diagnosis of hidden suppuration, such as appendicitis or an empyema, a persistent high leucocyte count is in favour of deep suppuration. It must, however, be remembered that there is no degree of leucocytosis absolutely diagnostic of pus, just as there is no clinical symptom or sign that in itself can warrant the diagnosis of a hidden abscess. A marked leucocytosis of over 20,000 certainly strengthens the probability of such a condition, but it must always be borne in mind that an acute inflammatory process without pus formation may produce a very high leucocyte count, and that an abscess may occur without any marked leucocytosis.

A leucocytosis may be of considerable value in excluding a condition in which leucocytosis is not the rule, provided we can exclude secondary complications. Thus in a disease accompanied by high fever in which the diagnosis is uncertain, a marked leucocytosis will tend to exclude such conditions as typhoid or paratyphoid fever, malaria, influenza or tubercle. Uncomplicated cases of such diseases have usually no increase of white cells.

These polynuclear cells have very varied nuclei, but these nuclei can generally be classified into five groups.

1. Cells with one nuclear (rod-shaped) mass, or two lobes joined by a broad isthmus.
2. Double nuclei connected by a thread.
3. Three segments.
4. Four segments.
5. More than four segments.

The cells with single or double nuclei are the young leucocytes, while those with four, five or more nuclear masses are beginning to age.

The percentages in normal blood are

No. 1, 6% ; No. 2, 35% ; No. 3, 42% ; No. 4, 16%; and No. 5, 1%.

The changes in the proportion of these cells, classified in this manner by their nuclear form, has been much studied, but it is especially in tuberculosis that this study has proved of value in diagnosis and prognosis. A deviation of the count to the left practically always occurs in active tuberculosis. The greater the deviation to the left the worse the prognosis, while, as the case improves, the deviation to the left disappears ; and the tendency to deviate to the right is always of good prognostic augury.

A great many workers have confirmed Ameth's results, and there is now no doubt that this is a useful method of blood examination in pulmonary tuberculosis.

In other diseases there is a relative or absolute

increase of the mononuclear cells. This is notably the case with malaria and kala-azar. It is said that in malaria the number of mononuclears may reach 90% of the total number of leucocytes. In such diseases the increase is mainly in the large mononuclear cells; and it is interesting to note that these large mononuclear cells correspond to Metchnikoff's macrocytes, and that there is good reason to believe that these cells have a special power of englobing debris and animal cells rather than micro-organisms. In an inflammatory process, say in the peritoneum of an experimental animal, they become progressively more in evidence as the conflict with the microbes begins to end, and their principal function seems to be the phagocytosis and absorption of dead or dying tissue cells, leucocytes and blood cells. It is thus very striking that in infections due to organisms such as the malarial parasite and the trypanosome these cells should be largely increased in contradistinction to what occurs in ordinary microbic infections. Dr. Eyre has made an interesting diagnostic use of this peculiarity of plasmodial infections. He believes that sympathetic ophthalmia is such an infection, and if, in a doubtful case, the large mononuclears of the blood are increased to 15% or more, he states that this is an indication that the eye should be removed. It is certain that in some cases where this diagnostic indication has been neglected by the ophthalmic surgeon disastrous results have followed.

In certain microbic infections, such as tubercle, we have also a relative increase of lymphocytes. In the formation of the tubercle nodule the polynuclears are first attracted in the very early stages, and afterwards the lymphocytes; so that the formed tubercle is composed mainly of mononuclear elements, with a tendency to the formation of giant cells, due to the fusion of mononuclear elements. A similar lymphocytic infiltration occurs in syphilis, and the blood of this disease presents a relative lymphocytosis In smallpox a mononucleosis is also the rule. In typhoid fever also the total number of the leucocytes is decreased, but there is a relative lymphocytosis. In this disease the lymphatic apparatus is specially involved in the morbid process. It has been stated that if animals that are hardly at all susceptible to the typhoid bacillus be infected artificially, that an intense polynuclear leucocytosis results and not a lymphocytosis.

A large amount of interesting work has recently been published on the effects of dry heat, X-rays and radium on the lymphocytes of the blood.

In animals subjected to dry heat, X-rays or radium, these cells showed at first a diminution in number, and this is followed by a large increase lasting for two or three weeks. This increase often amounts to a gain of 200 or 300%. The circulating lymphocytes in such cases may also show examples of amitotic divisions. It has also been shown that the characteristic decrease in the number of lymphocytes immediately after these forms of treatment is accompanied by an excessive cell destruction in the spleen lymph glands. For this reason it seems evident that the pronounced lymphocytosis afterwards induced by these agencies is due, at least in part, to the enhanced proliferative activity of germinal centres in the spleen and lymph glands, reacting to the initial destructive effect. Residence in the tropics and exposure to the sun's rays have also been shown to produce a marked increase in the circulating lymphocytes.

These observations are very interesting in connection with the effect of X-rays and radium on cancers and tumour growths. There seems a great deal of evidence to show that the lymphocytes are in some way connected with immunity to cancer.

1. Lymphocytes and related cells are found in abundance about a cancer graft in immune animals, and these cells are relatively absent round such a graft in a susceptible animal.
2. There is a greater tendency to lymphocyte proliferation in animals potentially immune to cancer.
3. A lymphocyte crisis in the circulating blood occurs in potentially immune animals after inoculation with cancer.
4. Animals immune to cancer grafts are rendered susceptible if at the time of the grafting the lymphocytes are banished by means of X-rays.
5. Established cancer immunity may be destroyed by similar means.
6. After artificial stimulation of the lymphocytes susceptible animals become immune to cancer.

Similar experimental work has been done with the object of showing that the lymphocytes are also concerned in resistance to tubercle. The literature of the subject seems to show that individuals who have recovered from tuberculosis show an increase in the number of their circulating lymphocytes. Blood counts on rapidly advancing cases of tuberculosis show a decrease of this type of cell. The blood changes, together with the fact that tuberculous lesions are characterised by an accumulation of a large number of lymphocytes, are suggestive of the part played by this cell in resistance to tuberculosis.

To this evidence is added the following

experimental results:– The lowering of the resistance to tuberculosis in animals depleted of their lymphocytes by means of X-rays, and the increased resistance in animals with their lymphocytes increased by three widely different methods – splenectomy, cancer immunity, and dry heat.

The variations of the eosinophile cells are also interesting, and sometimes of definite diagnostic value. As a rule, in infectious disease the eosinophiles almost disappear from the blood, but have a tendency to come back as convalescence ensues. In certain diseases of the skin such as dermatitis, herpetiformis and pemphigus, and also in parasitic infections they may be notably increased. In the case of intestinal worms the eosinophiles may be greatly increased. It has been shown that this is due to the substances secreted by these parasites. In the case of a hydatid cyst with no eosinophiles, the puncture of one of the cysts is followed by a marked eosinophilia. Extracts of parasitic worms produce marked eosinophilia when injected into mice or guinea pigs. It has also been observed that the eosinophiles collect round the walls of hyatid cysts.

Weinberg and Seguin have done some interesting work with extracts of ascaris lumbricoides. They have shown that a local injection of this extract produced a persistent local, as well as a general, eosinophilia: that this reaction is more intense when the animals get their second inoculation. It is thus quite clear from this short account of the different types of leucocytes that the enumeration of the leucocytes and their differential count may often give clinicians information of both prognostic and diagnostic importance. The value of such determination is, however, far from absolute, and the findings must be interpreted with due regard to the other clinical signs and symptoms of the case under investigation.

Widal and Ravant in this connection introduced a method of diagnosis and prognosis which they have called cyto- diagnosis and cyto-prognosis. Thus in a pleural effusion the presence of a large number of polynuclear elements signifies an acute, and, if the leucocytes go beyond certain limits, a purulent process; while a mononuclear lymphocytosis occurs in more chronic processes, which are frequently tuberculous. It is also true that as an acute serous inflammation begins to subside the polynuclears are replaced by mononuclear cells.

In the examination of the cerebro-spinal fluid, the cell count and its type have proved of very great prognostic and diagnostic value. A normal cerebro-spinal fluid has never more than ten cells per cubic millimetre. In acute meningitis, due to the meningococcus streptococcus and pneumococcus there is a large increase of polynuclear elements, while in tubercle and syphilis the cells may be almost entirely mononuclear. One of the first signs of successful antisyphilitic treatment in cases of cerebro-spinal syphilis is a diminution of the pleiocytosis, that is a decrease in the cell count of the cerebro-spinal fluid.

The leucocytes, especially the polynuclear cells, have many physiological properties of interest.

1. *Mobility*. We have already drawn attention to their wonderful power of amorboid motion. In a cold-blooded animal such as the frog, these movements may be studied under a microscope at room temperature, while in man and other warm-blooded animals a warm stage is required for this purpose. Dr. Graham and I have done a large number of experiments with leucocytes and pus cells. We find that the leucocytes will live for a considerable time at room temperature outside the body if kept in their native element. Thus, pus cells from a pleural effusion will be found alive after two or three days. They seem to die more quickly if they are washed and kept in saline solution, in ten or twelve hours. Their power of adhering, when alive, to a glass surface, as shown in Wright's experiment, is very remarkable. If blood be taken in a small capillary tube and put in the incubator the leucocytes attach themselves in large numbers to the walls of the capillary tube, the clot and blood serum can be blown out of the capillary tube, and the leucocytes adhering to its walls, when fixed and stained, can easily be examined under the microscope. This process reaches its maximum in from thirty to sixty minutes at incubator temperature. After an hour or longer the leucocytes begin to detach themselves from the glass, and this would appear to be due to some toxic principle developed as the blood-clotting changes are produced. If the clot be removed at a time when a large number of leucocytes have adhered to the glass, and replaced by serum separated from the clot, the leucocytes will remain fixed to the glass for many hours. This whole process takes place also at room temperature, but much more slowly.

Leucocytes in a suitable medium will adhere to the glass as long as they are alive. When dead they do not stick at all.

If washed leucocytes from the blood be suspended in saline they adhere much more quickly and in larger numbers if fresh serum be added to the mixture. Fresh serum will often increase the yield by four or fivefold or more. They act best in isotonic solution, and an increase of the saline concentration

prevents them from adhering to the glass. Pus cells act in a similar manner, but our experiments show that there are some notable differences. The cause of the abnormal behaviour of pus cells is still obscure. For instance, fresh serum always produces less difference in the yield of pus cells than occurs with washed leucocytes from the blood. Thus, if one part of washed leucocytes, prepared in the usual way, is mixed with two parts of saline on one of Wright's windows, while on the next window the same quantity of washed leucocytes and two parts of fresh serum are mixed in a similar manner, the yield on these two windows will be as 1 is to 5 or 10, while if pus cells be used in an identical experiment the proportionate yield will be seldom more than 1 to 2 or 3. A very remarkable result has been found with a considerable number of samples of pus that have been studied. Instead of getting an increase in the window containing fresh serum we may get a marked decrease, or none at all. To take an example, pus cells are taken and washed in saline, and in window No. 1 one part of these washed pus cells and two parts of saline are mixed, while in window No. 2 one part of the same pus cells and two parts of fresh serum are similarly mixed. The preparation is put in a moist chamber in the incubator for twenty minutes. The windows are then washed, fixed and stained. The saline preparation may be found to have a large number of pus cells adhering to the glass while the other preparation, containing fresh serum, may have none. This is a very extraordinary result. Is it of an anaphylactic nature?

Chemiotaxis. Leucocytes, especially the polynuclear variety, are attracted by numerous substances, especially microbic products. Numerous examples of this attractive power of soluble substances in amorboid cells are to be found throughout the animal kingdom. Often among the lower unicellular organisms these organisms are attracted by the substances which they utilise for nutriment. It is very probable that this property guides many parasites to the part of the body where they are usually found, and explains, at least in part, organotropy. For instance, the sporozoites of the malarial parasite are attracted to the salivary glands of the mosquito, and when inoculated by it into the human being they are attracted by and penetrate the red cell.

Massant and Ch. Bordet have systematically investigated this question of chemiotaxis. They used capillary tubes, some filled with uninoculated medium, and others filled with organisms such as staphylococci and streptococci. These were inserted under the skin of a frog. When these tubes were examined several hours afterwards, those containing the sterile culture mediums showed nothing, while those containing the organisms were found plugged to a considerable length with polynuclear leucocytes. If the organisms in these tubes were very concentrated no leucocytes were found. Also, if the animal was anaesthetised with paraldehyde the attraction of the leucocytes did not occur. There, therefore, appears to be a negative as well as a positive chemiotaxis. Hugensshmid has shown that saliva, always rich in organisms, has a powerful attraction for leucocytes. This peculiarity of saliva no doubt accounts for the fact that wounds about the buccal cavity usually heal rapidly although the saliva is full of organisms. If a very virulent organism is injected subcutaneously a strange phenomenon takes place: we have a marked effusion of plasma and vascular congestion without any diapedesis of leucocytes. This is an example of negative chemiotaxis.

The negative chemiotaxis of the leucocytes, which may be very marked, may be modified into positive chemiotaxis as the result of vaccination. This fact, one of fundamental importance, was first demonstrated for the immunity against anthrax. Massart studied the general subject and collected a series of data which led him to say that "vaccination effects an education of the leucocytes: these latter become so adapted that they can approach the virulent microorganism."The best method of forming an estimate of the change which the leucocytes undergo is by injecting subcutaneously very virulent organisms capable of setting up a generalized infection. The anthrax bacillus, Gamaleia's vibrio or streptococci, are suitable for such a study. These organisms, when inoculated subcutaneously into susceptible animals, set up a very slight local reaction or none at all, in the form of an exudation of transparent fluid almost entirely *without* leucocytes. The micro-organisms grow freely in these exudations, and soon invade the animal. In vaccinated animals the local reaction is more marked, and the exudation, very rich in leucocytes, is poor in fluid: the micro-organisms remain free for a very short time, being soon ingested by the leucocytes. Their destruction inside these cells takes a longer or shorter time, but in the end is complete if the immunity holds.

Phagocytosis. The mobility, tactile sensibility and chemiotactic properties of the leucocytes are characteristics which are essentially connected with its phagocytic power. The polynuclear leucocyte has

the power of englobing all sorts of particles, carbon or carmine particles as well as cells and micro-organisms. As a general rule, as has been pointed out, inert particles and animal cells are phagocytosed by the macrophages while the microphages or polynuclear cells direct their attention mainly to living or dead microbes. The phagocytosis of a comparatively large organism, such as a Trypanosome, is an interesting spectacle. The macrophage seizes one of its extremities and slowly englobes it, while the rest of the organism still free moves actively, as if resisting the process. If broth be first injected into the peritoneum of a guinea pig, and then an organism that is only feebly pathogenic, beautiful preparations of phagocytosis can be obtained. One can puncture the peritoneal cavity at intervals and thus study the progress of phagocytosis and intracellular digestion. If the organisms are very virulent the phagocytosis is much slower, or may not occur at all. Beautiful preparations of phagocytosis can be prepared in vitra by the use of Leishman's or Wright's techniques. Wright and Douglas, in a series of convincing experiments, showed conclusively that phagocytosis only takes place in the presence of active serum. Thus they demonstrated that if the serum be heated at 60° for fifteen or twenty minutes the process does not take place. They called this property of the serum the Opsonic power, and showed that this property of fresh serum could be destroyed by heat, sun, light, and that it gradually disappeared if the serum was kept. The opsonin acts upon the microbes, and thus prepares them for ingestion by the phagocytes. We have elsewhere pointed out that fresh serum has a stimulating effect on the amorboid movements of the leucocytes, and it may possibly be that the opsonin is the property of the serum that stimulates the amorboid movements, and that an organism charged with opsonin stimulates the phagocyte to throw out an amorboid process and englobe it.

The classic work of Wright on the opsonic index and its variations in infective diseases has thrown a wonderful light on the problems of immunity. He has shown that determination of the opsonic index may prove of great diagnostic importance, so that, given sufficient time and skill, it is possible for an expert worker to tell when a given microorganism is infecting the patient. This method is invaluable in scientific investigation, but as a practical clinical method it has fallen into abeyance owing to the fact that the technique of the worker must be developed to a very high degree, and the labour involved in such obsonic determination is very great. The criticisms that were hurled against the accuracy of the obsonic technique always reminded me of the man who, after a few weeks' practice, is able with difficulty to go round a golf course in some 150 strokes. When told that Vardon had gone round in 72 he remarked that this was utterly impossible and he could not believe it.

As the method is too laborious for clinical work its merit rests in the fact that for scientific investigation it often proves of great value, and because the work of Wright and his school has explained many of the obscure problems of infection and immunity.

To mention a few points:—

The low opsonic index in chronic and localised infections explains their persistence, and the fact that such cases are often benefited by therapeutic inoculation. The mechanism of immunization is in abeyance and the vaccine stimulates the latent powers of the organism. The continuous variation of the opsonic index in febrile conditions due to excessive auto-inoculation shows the need of rest as the only satisfactory way of lessening these inoculations.

In the course of an infection there is a time when the patient requires to rest and a time when he requires graduated exercises, massage, X-ray and similar therapeutic devices. The reason for all this is made clear by the study of opsonic determinations in such cases.

To take another example, the blood of a case of cerebrospinal fever has generally a high opsonic and agglutinating power, yet the infection goes on. The low opsonic power and want of agglutinins in the cerebro-spinal fluid explains the anomaly.

There is no piece of technical work that has unravelled more of the problems of infection. The language of infection is now the language of the opsonist, and the work of Wright has made an indelible impress on our conception of infective processes.

Some interesting work of Besredka shows the protective power of the leucocytes when poisons are injected into the organism. If trisulphide of arsenic be injected into the peritoneum of an experimental animal, the intraperitoneal inoculation produces a local leucocytosis, and the macrophages appear and take up the granules of arsenic and preserve the other tissues from this poisonous agent. It is true that the arsenic is slowly absorbed from the macrophages, but under these conditions only slight symptoms of poisoning occur. If, on the other hand, the phagocytes are embarrassed by the previous injection of carmine, which prevents the phagocytosis of the granules of

arsenic, the poisonous effects of the arsenic are quickly manifest, and the animal dies from an amount which under normal circumstances it would easily tolerate. If, again, before the injection of the arsenic the peritoneum of the animal is prepared by an injection of sterile broth, which causes a marked afflux of leucocytes, the resistance of the animal to the poison is greatly increased.

It has also been shown that leucocytes have the power of taking up soluble poisons such as potassium arsenito, soluble salts of iron and atropine. The leucocytes themselves have been shown to be much more resistant to poisons than most other cellular structures. It is thus seen that the leucocytes have marked power of protecting the organism against the action of numerous poisons.

Certain substances, such as calcium and small quantities of chloral, alcohol and camphor, iodide of potassium and iodoform stimulate phagocytosis. The absorption of diseased tissue is due to phagocytic activity. There is little doubt that the efficacy of iodide of potash in syphilitic and actinomycotic nodules is due to the influence of this drug on the phagocytic process.

INTRACELLULAR DIGESTION.

The fate of the infected organisms is often a process of digestion by the protoplasm of the phagocyte. It is frequently possible to see that a change is taking place in organisms phagocytosed. The rapidity with which this intracellular digestion takes place depends

(1) on the nature of the organism,

(2) on the source of the phagocytes.

The progressive sterilisation of pus is frequently observed. Samples of pus may be quite sterile, that is, the leucocytes or pus cells have killed all the organisms originally present.

Organisms that have been phagocytosed frequently show marked degenerative changes. They swell up, become granular and do not strain in the normal manner. This is particularly the case with Bacillus Typhosus, and to a lesser extent with coli, meningococci, pneumococci, etc. Metchnikoff has shown that the cholera vibrio is rapidly transformed into round granules when it is phagocytosed. The mononuclear cells have much less power to do this than the polynuclears. Phagocytosed organisms stain less distinctly than free microbes. They lose their affinity for basic stains and are stained with eosine. The fact that phagocytosed organs stain with eosine is very general. It occurs to a greater or less extent with such organisms as cholera, anthrax, typhoid, Friedluder, diphtheria, gonococci and streptococci. It only occurs when the organisms are englobed and a powerful bactericidal serum does not produce this effect.

Neutral red does not tint free bacteria, but phagocytosed germs are frequently coloured with this dye. Metchnikoff has pointed out that this reaction is due to acid digestion. Metchnikoff held the view strongly that the complement of alexine was the secretion of the phagocytes; that with certain organisms immune serum had the power of digesting them without any intervention of phagocytes was simply, according to his view, that the digestive juice of the leucocyte has escaped into the serum. This view, however, is probably not correct, as it is quite possible that different substances may have similar effects. Recent work has shown that the digestion that causes the granular metamorphosis of organisms in the interior of the phagocytes is not the same action that causes fresh serum to dissolve some varieties of organisms.

It has been shown that leucocytes contain ferments similar to trypsin, and there are many reasons for believing that the ferments contained in the polynuclear cells differ from those contained in macrophages. This conclusion is consistent with the fact that their phagocytic activities are different. Fresh serum has marked antitryptic powers, especially the serum of infected animals or men. Wright has shown that this high antitryptic power of serum has a certain inhibitory power on the growth of micro-organisms, but that the antitryptic power of liquor puris soon disappears owing to the fact that trypsin is liberated from broken-down leucocytes. When pus or serum thus become tryptic organisms grow in it very luxuriantly.

What is known as chloroform digestion of fibrin is due to the ferments contained in the leucocytes. The chloroform destroys the antitryptic power, and thus allows the tryptic ferments to act.

It has been shown by Metchnikoff that phagocytosis is almost universal throughout the animal kingdom. In the lower organisms that are not provided with a special digestive apparatus he has shown that phagocytosis serves two definite purposes – it is the mechanism by which unicellular amorboid organisms, and some even higher in the scale, utilise food stuffs and organisms for their nutriment; it is also a highly efficient method of defence against their microbic assailants – while in the higher animals, where there is a perfected digestive apparatus, the phagocytes no longer act as assimil- ators; their function seems to be that of defence alone. What, then, is the action of the

leucocytes on foreign albumens and nutritive materials if introduced parenterally into the higher animals? They are dealt with in much the same way as micro-organisms: antibodies and special ferments are quickly elaborated which facilitate their capture or their disintegration in the humours of the body. When in inoculations such substances are given, the cells of the body respond in a manner that may be far from physiological; in fact, in certain circumstances we may have all the symptoms of the acute shock which is called anaphylaxis, which frequently risks the very life of the animal. Thus, when, in nature, the phagocytes enter into conflict with foreign serums and albumens, it is as the result of accidental and injurious penetrations similar to the invasion of micro-organisms. Under these circumstances the phagocyte seems to have lost its ancestral role of absorbing nutriment from such albumenous materials; its function now is not to assimilate but to destroy.

THE BACTERICAL POWER OF THE PHAGOCYTE.

The beautiful experiments with leucocytes designed by Sir A. E. Wright demonstrate in a most convincing manner the power of the leucocytes to inhibit and kill micro-organisms. He centrifugalised defibrinated blood, which then consists of three layers: a layer of serum, a layer mainly of white cells, and a layer of red blood corpuscles. Drops were taken from each layer and fixed on an agar surface implanted with streptococci. Each drop is covered with a cover slip and the containing Petri Dish is incubated. Luxuriant growth appears on the serum and blood preparation, but not on the leucocyte preparation.

His glass lath experiment gives similar results. As I have already pointed out leucocytes have a powerful tendency to adhere to a glass surface. If a little strip of glass be inserted in a small tube of blood and the whole centrifugalised, and afterwards the glass lath removed and washed under the tap, the leucocytes can be seen forming a broad band in the middle of the lath, and getting fewer in both directions. We now impose the lath on an agar surface implanted with staphylococci or streptococci. Wright says, "Shall I tell you to what we can liken that experiment ? It is as if a great number of small slugs had attached themselves across a sheet of glass in the form of a belt, and we had then, leaving the slugs just space to move, laid down that pane upon a surface of earth thickly implanted with grass seed." You will appreciate that the slugs would round about them eat up the sprouting grass, giving us a bare band which would contrast with the green background of the surrounding field. Now that is exactly what happens with the lath experiment. We have across the middle of the lath a clean band of agar, and everywhere else a luxuriant microbic growth.

These experiments can be repeated with fresh pus. The pus cells act like the leucocytes and prevent the growth of, and destroy the organisms with which they come in contact.

This effect is not entirely due to phagocytosis, for if the leucocytes be thoroughly washed with saline to remove all traces of serum, almost the same bactericidal effect is produced, although in the absence of serum phagocytosis does not take place. These experiments are full of instruction; they tell us that if we want to kill microbes we must bring the leucocytes, and not the serum, to bear on the invading organisms. This is the secret of the brilliant success of primary suture in lacerated war wounds. When in the recent war the wounds were properly cleaned up by the surgeon and sutured immediately, they often healed by first intention, not because the surgeon removed all the organisms – this was impossible – but because he removed all devitalized tissue, and allowed the bactericidal power of the leucocytes fair play. What a miracle of healing nature can effect was impressed on me by the secondary suture of a large septic wound. This large wound had been dressed for some time and appeared fairly healthy, but still contained streptococci and staphylococci. The surgeon decided to attempt secondary suture. He sewed up this huge wound, and at one part put in a drainage tube. The next day the temperature rose to 103, and the pus coming through the drainage tube sinus, when spread on a glass slide and stained, contained countless millions of streptococci. The next day the temperature had fallen to normal, and the discharge from the same sinus contained practically no microorganism. This is what nature and the leucocyte can do when you have given them a proper chance. Wright has insisted that the healing of wounds is not to be accomplished by the use of innumerable antiseptics but by utilising the bactericidal power of the leucocytes and of the blood fluids to the best advantage. The physiology of healing and its proper applications must be studied. Nature's method is far more powerful, if it gets a chance, than any antiseptic. In the old days, when I was house surgeon in the Royal, and fresh from the Extern where, with sedulous care, I had treated many ulcers and sores with, as I thought, eminently satisfactory results, a patient with chronic ulcers on both legs was admitted to Mulholland Ward under Dr. T. K. Wheeler. The ulcer on the right leg was almost

identical in shape and size with that on the left. Dr. Wheeler said to me, "Now, lad, we will see what your dressings can do. Take any dressing you like and with it dress the ulcer on the right, and that on the left dress with nothing but boiled water in exactly the same way." From my experience in the Extern I at once chose red lotion. Both ulcers began to heal, owing to the rest and to the fact that they were kept clean, but they both healed in exactly the same time.

Sir George Makins was the consulting surgeon in our area in France, and at the meetings of the Etaples Society, it was his custom to sum up the salient points of any discussion that took place. The subject of the discussion was on this occasion the use of antiseptics in septic wounds. The subject was discussed ad nauseum: many advocated the so- called Dakon's solution; one of the older men advocated iodoform and glycerine, others carbolic, and so on. Sir George Makins finished his remarks by saying, "Remember, gentlemen, you cannot prevent a wound from healing, whatever you may do.[3]

The trend of Metchnikoff's great work was that immunity and healing were essentially due to the phagocytic action of the cells of the body, and that the blood fluids played only a secondary role. He modified his view somewhat when the German investigators with antitoxins, agglutinins, lysons and immune bodies, endeavoured to demolish his now celebrated thesis. In the main, however, he stuck to his original conception, defending it by a wealth of argument and experiment that has never been equalled in scientific literature. In the end we think that Metchnikoff had the best of the battle.

Let us consider for a moment the various reasons for Metchnikoff's view that phagocytosis plays the dominant part in immunity.

1st. There is always a direct parallelism between energetic phagocytosis and resistance. The immunized animal gives a better phagocytic response than an animal not so heated.

Defective phagocytosis means defective resistance. There is no example of cure in which the phagocytes do not play a part. The phagocytes, as we have seen, are endowed with wonderful properties which fit them for the struggle with micro-organisms – the meningococci and gonococci.

2nd. The blood fluids themselves have very little power of killing organisms; in fact the majority of organisms grow well in serum or plasma, and it makes little difference whether the serum comes from an immune or susceptible animal.

3rd. Experiment shows that when pathogenic organisms are injected in regions where the leucocytes are plentiful they are less dangerous than when they are inoculated at points where these cells are few. The rapidity of phagocytosis is of great importance as the microbes have not time to multiply and produce protective capsules. Inoculation into the aqueous humour is specially severe, and the pigeon normally refractive to anthrax contracts this disease when the virus is injected into this region, as here the leucocytes are few and collect slowly. For the same reasons, a rabbit immunized against streptococci does not tolerate in this region an inoculation of streptococci which is harmless subcutaneously. One can always increase the resistance of the peritoneum by injecting fluids which produce a local leucocytosis. Isaeff has demonstrated that not only normal serums but a whole series of fluids, such as broth, wine, etc., exert a protective influence against microbic infections. These fluids should be injected about twenty-four hours before the introduction of the bacteria. In this way an animal will acquire an immunity against absolutely fatal doses of cholera vibrios. These experiments have also been verified with the typhoid bacillus and with the streptococcus. The injection of peptonised broth into the peritoneal cavity of the normal guinea pig, made twenty-four hours before an inoculation of double the fatal dose of streptococci, protects the animal. These fluids manifest their influence by increasing phagocytic activity. It is during this period of greatest phagocytosis that the animal exhibits the most marked resistance against infective micro-organisms. Because of these striking results with experimental animals it has been suggested that a surgeon might protect the peritoneum against infection by injecting in this region a few hours before operation suitable liquids, such as broth, horse serum, etc., to subjects on whom he intended to do a laparotomy. Besredka has also shown that this procedure protects the animal against the poisonous effects of arsenical compounds. This form of protection is local and non-specific. This principle may explain some anomalous points in immunity. It is probably due to local immunity that a faruncle may heal in one region while a second faruncle is developing in another. A patch of erysipelas will extend at the periphery while the centre heals. Protective results have also been obtained by injecting leucocytes along with a dose of microbes, and this method has also been applied in treating disease in animals and man, and the results tend to show that good results have been obtained.

4th. All factors which tend to depress the activity of the leucocytes diminish the resistance to infection. The spores of tetanus are easily phagocytosed, but

lactic acid favours the development of tetanus. This substance paralyses the leucocytes and prevents their response.

The injection of quinine has been known to produce tetanus. This is not due to want of sterility in the injection but to the fact that quinine is toxic to the leucocytes. Sir David Semple has fully investigated this point. Pure tetanus spores when injected under the skin do not produce tetanus, but if they are injected with other organisms or inert particles, tetanus results. No doubt these agents act by embarrassing the leucocytes in their struggle with the virulent agent. Opium has been shown to diminish the activity of the phagocytes, and in many cases it favours infection.

The dog is normally resistant to anthrax injection, but it contracts the disease if fine, inert particles are injected into the circulation.

Contusions and injuries favour infection, as in such conditions the phagocytes are already fully occupied in removing and absorbing the debris. Their afflux may also be interfered with by the injury and damage to the vessels. Cold, as we have seen, diminishes notably the activity of the leucocytes. Many infections are favoured by cold.

Inanition favours infection and causes a leucoplenia.

5th. As a general rule a marked leucocytosis is a favourable sign in an acute infection, such as pneumonia. If animals are immunized, the leucocytosis which results from their inoculation with organisms is very pronounced and lasts a long time.

Some recent experimental results have an important bearing on the fundamental role which the white cells play in processes of immunity. Wright, when working with pneumonia on the Rand in South Africa, endeavoured by opsonic and other methods to determine why the natives on the Rand were so susceptible to pneumonia, and also to determine the proper therapeutic and prophylactic doses of vaccine. Although thousands of opsonic indices were done the method proved unsatisfactory, due to the great variations in the opsonic indices, found not only among the natives but also among the European controls. Another method was therefore used, which gave very suggestive results. I have told you how, if fresh blood be drawn into capillary tubes, the leucocytes are deposited in vast numbers on the walls of the capillaries. Wright's method was as follows:—

A certain strength of pneumococcus emulsion was drawn into a capillary tube and drawn out again. A certain amount of the fluid adheres to the capillary wall, and this contains pneumococci. Wright has shown that this quantity is approximately of the capacity of the capillary tube. Into this washed capillary tube whole blood is drawn from the finger and incubated after sealing the tube. After a certain time the contents of the tube are examined for live pneumococci by cultural methods. He thus obtained with the blood of European controls a destruction of pneumococci equivalent to a destruction of 600,000 to 1,000,000 pneumococci by l c.c. of blood, whereas when working in the same manner with the blood of tropical natives no appreciable bactericidal effect could be demonstrated. Here was a test tube explanation of why the native is so susceptible to the pneumococcus. With defibrinated blood or with serum he obtained no such effect. He, therefore, concluded that the phagocytes are an essential factor in the bactericidal action of the whole blood on the pneumococcus.

Reist and Solis-Cohen, working with whole blood in vitra, with a technique similar to that of Wright, obtained some very interesting results. During the incubation of their capillary tubes, made from the freshly drawn blood of laboratory animals,, some bacteria were found to multiply while others did not. The growth of these latter bacteria was either inhibited or they were killed by the fresh blood. This inhibition of growth was not found if defibrinated blood or serum was used in similar experiments. They thus showed that the virulence of the pneumococcus was in direct proportion to its power of growth in the animals' blood in vitro. When the virulence of the pneumococcus was increased the power of growth increased. Thus the bactericidal power of a sample of whole blood is an index of the immunity of the species from which the blood was drawn. To take an example, the pigeon is immune to the pneumococcus, while the rabbit or mouse is highly susceptible. The blood of the pigeon used in this way killed a large number of pneumococci, while that of the rabbit or mouse killed very few. This remarkable series of experiments was fully established by workers in the Rockefeller Institute, and they showed that the essential factor in these experiments were the leucocytes. The results were not obtained with serum or defibrinated blood, which is largely deprived of its leucocytes, but were obtained with pneucocyte cream. These, worked also independently, showed that the power of the whole blood of the different animals was in direct relation to their known resistance to the pneumococcus.

I think we must admit that Metchnikoff's view, that the leucocytes are a dominant factor in immunity, is fully justified.