HISS LEUCOCYTE EXTRACT IN COMPLICATIONS OF NASAL AND AURAL SURGERY.*

DR. W. H. HASKIN, NEW YORK CITY.

In 1910, my associate, Dr. J. G. Dwyer, published a most valuable paper on the use of vaccines, serums and the Hiss leucocyte extract, and it is with the further use of this extract that this paper will deal. In the death of Prof. Hiss the profession has lost one of its most brilliant, enthusiastic and scientific members. His first report on this extract was published in the *Journal of Medical Research*, in November, 1908, and gave in detail the results of his experiments and the exact method for the preparation of the extract. His work had extended over a period of two years, so that even in his first paper he only offered a thing that had actually been tested and had given results.

It has been asked a thousand times, "Why hasn't he published his further work?" The only answer is that he was almost totally deaf and suffered with the extreme diffidence that these unfortunates so often have, and also, it is probable, that he knew that he was a doomed man for nearly four years, dying as he did from multiple melanotic sarcoma, which had destroyed one eye about a year and a half before his death. He has left a monument with us which is sure to prove one of our greatest mainstays. It may be that his extract as prepared to-day will not continue in use, but there is no question but that the principles upon which he worked and formed his theories are absolutely logical and that any further investigations along this line will be the direct result of his legacy, and therefore credit should be given him for his discovery. After his assistant, Dr. Hans Zinnser, went to California in 1909, Prof. Hiss became still more diffident and retired almost entirely into the seclusion of his laboratory. He told me several months before his death, that had not Dr. Dwyer come into his life, any further work with the extract would probably have stopped in 1910. A very strong friendship arose between them in 1910 and for the first time Prof. Hiss had a man follow up the clinical use of his preparation in whom he had entire confidence so that the many trials in actual practice have been due to Dr. Dwyer's enthusiasm and devotion to Prof. Hiss who never would go out to see a case himself but always sent his

*Read at the nineteenth annual meeting of the American Laryngological, Rhinological and Otological Society, Washington, D. C., May 8, 1913.

new-found friend. As Dr. Dwyer has been with me both in my office and hospital work ever since he entered practice, it is very natural that I, too, have become an ardent believer in the efficacy of this product, and have asked to read this paper only after being told that it could not be presented by Dr. Dwyer to whom so much of the credit is due for the brilliant results that have been procured.

It is necessary to read Prof. Hiss' theoretical considerations which led to his experimental work upon leucocyte extracts and infections, in order to fully understand the rationality of his work. He says that: "In thinking over this work I came to the conclusion that in many diseases we are probably dealing with an immunity a large part of whose mechanism is individually cellular, not only in the sense of phagocytosis and digestion, but in the neutralization of poisons given rise to by the disintegration of the bacteria—a mechanism in which the protecting cells must intervene and unaided by bodies in the plasma neutralize within themselves the poisonous products of the invading micro-organisms. It was this thought that gave rise to the further idea of aiding the leucocytes by furnishing them as directly as possible with the weapons which were being taken away from them in their fight with invading micro-organisms and to thus protect them from destruction and give them an opportunity to recuperate and carry on successfully their struggle against the invading germs. These weapons, whatever might be their nature, I assumed might possibly be furnished by an extract of the active substances of the leucocytes themselves (substances not ordinarily given up to the plasma or serum) and I also assumed that extracts would be more efficacious than living leucocytes themselves, introduced into the infected animal, since being diffusible they would probably be distributed impartially to all parts of the body by the circulatory mechanism and, as quickly as absorption would permit, relieve the fatigued leucocytes and protect, by any toxin-neutralizing or other power they might possess, the cells of highly specialized functions.

This idea of immunity differs from one that simply assumes the cells as the source of all immune bodies (which logically seems to be the case) in that it takes into consideration the presence and production in the leucocytes of agents which are not normally given up to the plasma, but which are constantly able to reproduce themselves and carry on the functions of digestion or neutralization simply for the benefit and protection of the individual cell, while not

being secreted or excreted by the cells for the more general benefit of the cell community at large.

"Thus we have a differentiation of immune agents into those which by virtue of their liberation and over-production by the cells, such as the anti-toxins, amboceptors, and agglutinins, etc., are free in the plasma and thus, when active, are immediately available for the protection of all the body cells; and into those agents by which certain cells primarily nourish and protect themselves, and are only of benefit to the cell community at large by virtue of the direct intervention of these cells between the invading germs and their products and the highly specialized cells requiring protection. It seems, then, that when these sources of protection are overtaxed or fail to act efficiently, on account of some inherent weakness or untoward circumstance of location, that the most reasonable course is, if possible, to support the chief army of attack as indicated by a study of the exudates and pathological changes in the disease in man and animals, and to endeavor to supply those products which are most heavily taxed in the fight, in other words, to introduce into the infected animal or man the substances composing the chief cells or all the cells of an exudate in the most available form and as little changed by manipulation as possible. Such substances, if they become free from the cells by extraction, might serve to neutralize poisons in the blood, might alone or in combination with bodies already in the blood act deleteriously on the bacteria, and thus protect and augment the activities of the flagging leucocytes by supplying them with their own weapons in the fight against the invading organisms. And further, the extracts of such exudates from previously immunized animals might even better serve this purpose, since their cells probably have, in their own fight against the same organisms gained increased powers, as is evidenced by the ability of such immunized animals to safely dispose of immense numbers of organisms without serious harm or loss of weight. Also, as a further adjuvant, immune sera might be found serviceable in some cases, especially early in the disease and when non-immune cells are being used, although it is our belief that sufficient immune bodies (bactericidal or bacteriolytic) are often present, and in sufficient amount even early in the disease, if the animal economy has not been entirely overwhelmed by an enormous primary dose of the infecting organisms or their poisons."

His paper gives the results of the curative influence of the extract in animals with staphylococcus, streptococcus, pneumococcus,

meningococcus and typhoid bacillus; it also reports the result of its use in twenty-four cases of meningitis in man, and its use in acute lobar pneumonia in man.

His original results have been so fully borne out since then in over 400 cases of various infections, most of them desperate ones, that it seems as though the time for doubt has gone and that we should all learn when and how to use it to the best advantage of the patient and not turn to it only as a last resort. Even a month ago two of our most prominent otologists asked me to tell them about this vaccine. It is not a vaccine or antitoxin in any sense of the words and should not be confused with them as is constantly done. My own experience with three desperate cases, all being in the hospital at the time, gives most marked evidence of its value.

Case 1: On February 18, 1913, Sol. Z., aged 1 year, was brought to my office, being referred by Dr. H. S. David. The child had been very ill for over five weeks running temperatures up to 105° , and with both ears discharging very profusely. The physician in charge had opened the drums several times, but failed to realize the gravity of the case and Dr. David, being a friend only, advised the parents to see me. Examination showed undoubted involvement of both mastoids, with extreme contraction of both pupils and a very suspicious, rigid contraction of the muscles of the neck. He was sent to the Manhattan Hospital at once and operated upon within two hours. Both processes were completely disintegrated and the sinus on the left side appeared to be almost necrotic for about half an inch. An attempt was made to draw off some spinal fluid but the syringe filled with blood, or at least a dark fluid which coagulated very rapidly. At the time this gave us some uneasiness, but Dr. Ende, of the Central Islip Hospital for the Insane, assured Dr. Dwyer that this was not an infrequent occurrence in his work at the hospital, and I have seen another such case since then. Blood was drawn during the operation for culture and proved to be negative. All possible speed was used, in order to lessen the shock as much as possible, and the patient was taken off the table at the end of thirty-five minutes. That night the temperature rose to 106° and the leucocyte extract was given and continued daily for seven days.

The temperature became lower, but remained around 102° for several days. A pediatricist was called in on the seventh day to determine whether there might not be some general systemic condition that was keeping up the temperature, but he found nothing. The child improved slowly but on the twenty-fifth day a large

trophic slough was discovered over the torcula and a day later another smaller one appeared near it on the left side. Up to this time both mastoid wounds had been doing very well, but then healing seemed to stop and the granulations became very flabby and unhealthy. The extract was again administered for three days with remarkable effect, both the wounds and the sloughs assuming a healthy appearance and going on from that time to complete healing at the end of the fifth week. This brief report cannot convey any idea of the desperate conditions we had to deal with and that the child recovered is entirely due to the power of the extract in giving strength to the overtaxed body of this profoundly infected child.

Case 2: John K., aged 2 years, was brought to Dr. McKernon's clinic on March 19, 1913, with a large subperiosteal abscess of ten days' duration, and was operated upon the same afternoon (*staphylococcus aureus*). His temperature at the time of operation was 103°, but fell to normal the following day and remained there until the fourth day. He then became suddenly ill and the temperature rose to 104°, pulse 136, and respirations 38, and this was accompanied by a constant cough. An examination of the chest showed marked crepitations over the lower right lung and a blood count showed 43,000 leucocytes, 75 per cent polynuclear and 25 per cent mononuclear cells. Ten cc. of the extract was given at once and repeated on the next day. It sounds like a fairy tale for me to tell you that the temperature fell at the end of forty-eight hours and that the lung conditions cleared up without going on to consolidation, but that is what happened and the same thing has happened in two other cases in which Dr. Dwyer was called and administered the extract. This child recovered rapidly and the mastoid wound was healed at the end of the third week.

Case 3: This case is the most remarkable, however, as it shows the cure of a *streptococcus capsulatus mucosus* bacteremia without operative measures. Jacob P., aged 6 years, was brought to Dr. McKernon's clinic on February 19, 1913, with the history of pain in the right ear of several days' duration but with no discharge. The previous history was negative. His father said that he had been having high fever and when seen the temperature was 104°. As there was no vacant bed in the hospital, a paracentesis was performed but no fluid escaped, although the membrane was very red and had appeared to bulge. On the following day he was admitted into the hospital with a temperature of 104°. The pain in the ear

had subsided and there was no tenderness over the mastoid, nor was there any thickening of the canal walls or other indication for operation except the high septic temperature. His blood count showed 16,000 leucocytes with 76 per cent polymorphonuclear and 23 per cent mononuclear cells. On February 19, he complained of severe pain in his left shoulder but this shifted to the right hip and groin on the next day, and Dr. Hutton, the attending physician, was asked to examine him. He reported: "That in the absence of any history it appeared to be a case of inflammatory rheumatism, but that the possibility of periostitis and osteomyelitis were not remote possibilities." Sodium salicylate was given for three days but without any effect. On February 21, the blood count showed 25,000 leucocytes, with 71 per cent polynuclear and 29 per cent mononuclear cells. A blood culture was ordered, but owing to some error was not taken until February 23, at which time the blood count showed 24,000 leucocytes, with 81 per cent polynuclear and 19 per cent mononuclear cells.

On February 22, a marked endocarditis was discovered affecting the aortic valves. Dr. Phillips saw the case with me, being the only surgeon in the hospital at the time, and advised against any operative measures. I should say that Dr. Rac had seen the case with me on two occasions and had also advised against operating, as we had nothing but the high temperature to indicate involvement of the mastoid. By February 23, there was marked thickening around the right groin and Dr. Berg, of Mt. Sinai Hospital, was called to see him. He found the condition to be a profound sepsis, but advised against any operative procedure at the hip for the time being at least. On February 24, our pathologist reported a marked bacteremia, the cultures showing numerous growths of an hemolytic streptococcus, this was later differentiated as the capsulatus mucosus. The leucocyte extract was then given daily in 10 cc. doses. An improvement was at once noted and there was a daily drop in the temperature, as shown by the chart. On February 27, the leucocyte count showed 11,500 leucocytes, with 75 per cent polynuclear and 25 per cent mononuclear cells, this being a most remarkable change showing the increased resisting power of the blood by the decrease in the total leucocytosis as well as the decrease in the polynuclear and the increase in the mononuclear cells, which Prof. Hiss claimed to be the most active bodies in resisting invasion by organisms. On February 28, after only five days use of the extract, a blood culture was found to be absolutely negative, even

after forty-eight hours in the incubator, on four different media. On March 2 and 3 he was given more of the extract although there was no special indication, it being administered to aid the leucocytes in their efforts in throwing off the results of the profound sepsis which had been present.

On March 6 another blood count and culture were made and proved that the bacteremia had been overcome without any doubt, the culture being again absolutely negative, and the differential count showing a still further improvement, as follows: leucocytes, 13,000; polynuclears, 67.5 per cent; mononuclears, 31 per cent, and 1.5 per cent transitional forms. With this improvement in the character of the blood there was a corresponding change in the child himself. The heart murmur had almost disappeared, his appetite was good, he was happy and became a ward favorite with his sunny smile and good nature; but although all the swelling around the hip and groin had gone, he could not bend the hip to sit up, complaining of severe pain. On March 21, Dr. Phelps kindly applied a plaster casing around the body and the right thigh and after another blood culture and count showed well, (that is, good resistance and negative for bacteria), he was discharged and was taken home. Just what was present in or around the hip no one could say. An x-ray showed nothing and an exploratory puncture was unsuccessful in withdrawing any fluid. This case is remarkable and also unique in that it is the only case on record, so far as I know, of a cure of an actual streptococcic bacteremia without any operative measures having been used. There is no doubt but there would have been a fatal result in this case had it not been for the efficacy of the extract, for no one can appreciate the actual profound sepsis of the patient except those who watched him from day to day.

It was felt that two of these cases would terminate fatally, and the abortion of the pulmonary consolidation in the third was a most unusual and unexpected ending. As the extract was the only remedy used in all three cases, their recovery was surely due solely to its influence. In two other cases of pneumonia, occurring in the practice of other physicians, the attacks were cut short in much the same manner as in the one reported above, the extract being administered very early in the attack, so that it seems as though its future use, when given early enough, will prove a great blessing. Dr. Dwyer has kindly prepared a record of cases in which the extract has been used in the practice of a large number of physicians.

each of whom have sent in their bedside-notes with the reports of their cases. He personally saw most of the cases before giving the first dose, and the writer has marvelled at the recovery of many of them after hearing of their original condition.

In erysipelas and in true lobar pneumonia it acts in many cases as though it were a true specific, the relief to the patient being felt very quickly after the first injection. It should not be necessary for me to say that it is not, strictly speaking, a specific for anything. There is invariably a fall of temperature with a marked improvement of the heart beat. Delirium generally disappears rapidly and the patient tells of his relief and feeling of increased strength from the beginning. During the past year over 1,000 rabbits were used, each giving an average of 30 ccm. of the extract. As the average dose has been 10 ccm., this will give some idea of how extensively it has been used, and I wish it were possible to read some of the many personal letters that have been sent by the physicians who have used it. Even the faculty of the College of Physicians and Surgeons, in whose laboratory all of the extract has been prepared, had no idea of the extent to which it had been used or of the brilliant results obtained, until after Prof. Hiss' death and Dr. Dwyer was asked to give them a full report of the work that had been done. For years Prof. Hiss bore the entire expense of preparing and furnishing his preparation, for he refused to proclaim his work until clinical results would prove its value. It should be borne in mind that this is not, in any sense, either a vaccine, anti-toxin or specific. It has no connection whatever with any bacteria, but is purely a physiological extract and emulsion of the leucocytes themselves, which, on being injected into the cellular tissues, is taken up into the circulation and furnishes food to the overtaxed and exhausted leucocytes in the body, thus allowing them to renew their fight in overcoming the effects of the toxins and even the living organisms which may be present in the system.

The necessary dosage for any one or for all cases cannot, as yet, be given definitely. No two cases ever present exactly the same clinical pictures, so that each case must be a problem in itself and the successful use of the extract will depend upon an intelligent administration after careful examination of the heart and in many cases upon the correct interpretation of a differential blood count, which will always show the resisting power of the blood. The writer feels that a large number of patients would be greatly helped in their convalescence, if careful counts were made frequently and the extract were administered whenever diminished resistance was

shown by such counts. One important factor in its favor is that it has never been known to have produced any bad effects; it invariably increases resistance, and even in those patients who have not been saved the fatal end has been delayed many days. No medicine has ever been put to more severe tests than has this extract, Dr. Dwyer not being called to see the cases, generally, until they were almost *in extremis* and it was felt that nothing could save them.

Now that proof of its great value in most desperate cases is undoubted, it is to be hoped that the rationality of its use will be recognized by all, and that the many laboratories connected with our hospitals will take steps to prepare the extract for themselves and so be able to keep a supply constantly on hand to be used, not as a last resort, but to prevent the complete overpowering effects upon the patients of toxins or bacteria, and their products, that, with the aid of the extract, he should be able to throw off before his resistance becomes so lowered that nothing can save him. The method of preparation was given in detail by Prof. Hiss in his first paper, that of 1908, and is practically the same at the present date except that it has been found that it could be put out in twice the original strength without injury to the cellular tissues and for the past two years that has been done.

Dr. Dwyer has kindly prepared the following table: "This series of 39 cases occurring in nasal and aural diseases have been treated with the leucocyte extract: 1. Sinus-thrombosis, without positive blood-culture, 11 with 9 recoveries and 2 deaths. 2. Sinus-thrombosis with streptococcus in the blood-culture, 3 recoveries and 2 deaths. 3. Sinus thrombosis with streptococcus mucosus capsulatus in the blood-culture, 1 ending in death. 4. Septicemia: (a) Streptococcus mucosus capsulatus, 1 ending in recovery; (b) streptococcus pyogenes with acute endocarditis, 3 and all recovered; (c) pneumococcus, with acute middle ear, pneumonia and endocarditis, 1 case with recovery. 5. Clinical septicemia with endocarditis, following mastoiditis, 3 cases with 2 recoveries. 6. Meningitis: (a) Serous meningitis, 3 cases all recovered; (b) purulent meningitis, with the organism demonstrated in the cerebro-spinal fluid, 3 deaths and 1 recovery. 7. Mastoiditis complicated by pneumonia, 3 cases, all recovered. 8. Frontal sinusitis, complicated by clinical meningitis, 1 case with recovery. 9. Streptococcus sore throats, 5 with quick recovery in each.

This series is limited strictly to aural and nasal diseases and their complications, but in addition to the above we have a whole series of cases of septicemia and such conditions due to infections in other

parts of the body and our results on the whole are just as favorable.

We have, besides, a series of 148 cases of all kinds of erysipelas and will give the analysis of the results obtained in this series of cases.

STATISTICAL ANALYSIS OF ERYSIPELAS CASES.

Age of Patient	No. of Cases	Time of Treatment		Average Duration of Treatment	Termination of Cases	
		Early*	Late		Recovery	Death
Infants (up to 1 year).....	12	Early* 5	Late 7	4 days	3	2
Children (1-15) years)	14	Early 5	Late 9	1.5 days	5	
Adults (15-50 years)	110	Early 44	Late 66	3 days	9	
Over 50 years.....	12	Early 5	Late 7	2.2 days	44	
				3.5 days	66	
		Early 5	Late 7	1.5 days	5	
				3.7 days	6	1
Total	148	Early 59	Late 89	2.3 days	57	2
				4.05 days	86	3

*Early—Treatment begun within three days of appearance of lesion.

Late—Treatment begun later than three days after appearance of lesion.

RECAPITULATION.

Total number of cases treated—148; recovered 143; mortality 3.39%.

General average duration of treatment—3.18 days.

Number of recoveries under 1 year old—8 out of 12.

Per cent of recoveries under 1 year old—66.6%.

General mortality rate—(all cases) 3.39%.

Mortality among patients over 1 year—73%; recoveries 99.27%.

40 East Forty-first Street.

Carcinoma of the Tongue Following Epidermolysis Bullosa (Dystrophic Form). KLAUSNER. *Arch. f. Dermatol.*, Bd. 116, Heft 1, 1913.

In a girl of 25 years suffering from epidermolysis bullosa, carcinoma of the tongue developed. The author feels that supersensitiveness and disturbances in the anlage of the epithelium which occasionally, in cases of epidermolysis bullosa, lead to thickening of the mucous membrane or leucoplakia were in this case responsible for the glossal carcinoma.

ED.