In the faeces of only one case a bacteriophage of slight virulence for *B. typhosus* was isolated previous to the administration of bacteriophage. Within twenty-four hours of administration, however, an extremely virulent bacteriophage was obtained from all patients. Coincident with the presence of an active bacteriolytic agent in the faeces there occurred a rapid disappearance of *B. typhosus* from the faeces of six out of the seven patients. The course of one case (Case VII) was complicated by an infection of the urinary tract due to *B. typhosus*, and on several occasions when the faeces were obviously contaminated with urine *B. typhosus* was found. A sample of the urine obtained from this case within the first twenty-four hours after the administration of bacteriophage was examined for the presence of bacteriophage, but no active bacteriolytic agent could be demonstrated. The case had repeated subcutaneous injections of bacteriophage, but this did not apparently influence the typhoid bacilli present in the urinary tract. The disappearance of the bacteriophage from the faeces coincides very closely with defervescence except in Case VII, who had repeated doses of the lytic agent. The administration of bacteriophage subcutaneously and by mouth has so far proved to be a perfectly harmless procedure.

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THE PRECIPITATION OF CRISIS IN THE TREATMENT OF PNEUMONIA.*

BY

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THE hypothesis is accepted that pneumonia, either secondary to influenza or primary from so-called chill, is a manifestation of a suddenly lowered resistance to a germ or germs, normally present in the respiratory tract, which, in consequence of that lowered resistance, suddenly become pathogenic.

In 1922 I published with Dr. James Graham Willmore¹ a paper founded on observations made in the 17th General Hospital in Alexandria in 1918 and 1919 during the great pandemic of influenza and towards its close. We based our treatment on the fact that the white cell blood count of cases of influenza is low and remains low after the fever has ceased and for about five days after that, after which there is a sudden reactionary increase, usually about the tenth day of the disease and the fifth day of convalescence.

It is during this period of depression and lowered resistance, the result of or the cause of the leucopenia, that the danger of secondary infection exists, and we showed that an injection, either subcutaneously or intramuscularly, of sodium nucleinate in solution precipitates the reactionary increase of white cells in the peripheral circulation and so reinforces the patient's resistance. Sodium nucleinate, given in this way, greatly increases the white blood count whether the patient has a leucopenia or not, and in a normal individual it about doubles the white cell count in twenty-four hours. In cases of marked leucopenia in severe influenzal pneumonia counts have been seen to rise from 3,200 to 18,300 three days after a nuclein injection, with corresponding improvement in the patient's condition from a practically moribund state to one of convalescence in the same period. The toxic symptoms of many of the cases suggested an acidosis, and intensive doses of sodium bicarbonate were given either by mouth, bowel, or intravenous injection, together with glucose in the food or by bowel.

The success which attended our efforts in the pandemic

period was so marked that when I returned to general practice I invariably treated all cases of pneumonia on the same lines, with what I believe is an equally satisfactory result—that is, in every case of definite lobar pneumonia so treated a crisis has occurred about forty-eight hours or so after the first dose of sodium nucleinate was given, no matter what day of the disease it was administered.

I have not made a regular practice of making blood counts in all my private patients, but in those cases in which I did I found the white count little more than normal with the patient seriously ill from pneumonia.

The Egyptian cases were 32 in number and cover a period of some six weeks only; they are not selected, but only one of us kept records, so that at least double that number were similarly treated within that period. The English cases consist of 21 consecutive cases over a period of three and a half years. Records of 53 cases in all have therefore been kept, all of which responded to treatment except 8. All the patients were seriously ill, all had pneumonia, all had definite lobar consolidation except 7 cases of bronchopneumonia, nearly all had blood-stained sputum; this often appeared after the so-called crisis, indicating that the severity of the disease was arrested early. Many showed signs of acid toxæmia. All were treated as above described with sodium nucleinate injections. Most of them had as much as half a drachm of sodium bicarbonate every four hours; some had a full drachm. Those who had purulent sputum had an emulsion of creosote and potassium iodide. Cardiac and respiratory stimulants were given if indicated.

Of the 8 fatal cases, 2 were of patients with bronchopneumonia; the other 6 were war-worn soldiers in the pandemic period; 4 had nephritis to a marked degree which was not recent. All were in a very toxic condition on admission to hospital. Two were proved to have white blood counts under 4,000; one was as low as 1,900. Four had no special alkaline treatment, as they occurred before we appreciated its value, and therefore really ought not to be included in this series. One had dysentery and two had malaria.

Three of the patients who suffered from lobar pneumonia relapsed, sustaining a fresh invasion of lung area, but in all the temperature fell again by crisis within forty-eight hours after a further injection of nuclein. All the English cases of lobar pneumonia responded to treatment and recovered.

It will be seen that the cases of bronchopneumonia did not respond so typically as did those of the lobar type. They fell by lysis rather than crisis. It will be seen also that, if we eliminate from the series all the cases of bronchopneumonia and also all the cases which did not receive intensive alkaline treatment, we also eliminate all the fatal cases but two, which were moribund on admission, and had chronic conditions of nephritis before contracting pneumonia.

I do not for one moment claim that all these cases would not have recovered with ordinary expectant treatment, but I think it is at least worthy of note that in all the cases here reported of lobar pneumonia, fully treated, the patient's condition began to improve at once after the nuclein injection, that all of them experienced a sense of well-being the next day, and that in every case the crisis occurred from forty-eight to sixty hours after the first injection of sodium nucleinate.

The preparation used for intramuscular injection is a solution of sodium nucleinate put up by the Clin Laboratories of Paris in ampoules of 2 c.cm., containing 0.05 gram per cubic centimetre. The British agents are F. H. Mertens, 64, Holborn Viaduct, London, E.C.1.

The accompanying diagram shows the length of fever of forty successful cases of lobar pneumonia. The vertical lines represent the duration of the pyrexia, and the horizontal lines the nuclein injection, showing that the effect of the treatment in precipitating devolution is independent of the duration of the illness. In the three charts the heavy black line represents the temperature, while the dotted line represents the white cell count, the normal count of about 7,000 corresponding with the line of normal temperature. The leucocytic increase will be seen to be coincident with

* A paper read before the Liverpool Medical Institution, April 3rd, 1924.

the fall of temperature and the general improvement in the patient's condition.

Two typical cases are also reported in detail.

CASE I.

Sergeant F., aged 29, was admitted from his unit on December 8th, 1918; he had felt unwell for three days. His face was flushed and slightly cyanosed; there was general malaise and coughing, but no expectoration. The abdomen was tumid; he complained of subcostal pain on both sides. Temperature 102°, pulse 100. He was treated with sodium salicylate and stimulants. Two days later his condition showed some improvement; he had less pain; temperature 100°. On December 12th he was not so well: the cough was more marked, and the cyanosis increasing. The next day he was much worse—cyanosed, toxic, and stuporous. On December 14th he looked as if he were going to die. The white count was 3,200; temperature 104°, respirations 60. Sodium nucleinate was injected intramuscularly, and 30 grains of sodium bicarbonate given every four hours. Camphor was given hypodermically, alternating with digitalis 1/100 grain. The day following this treatment he was somewhat more easy; the white count was 7,200. Nuclein repeated. On December 16th he was much better, and was clear mentally; he was expectorating blood-stained mucus; temperature 101°. On December 18th the temperature was normal; he was breathing easily and slept well. The white count was 18,300. He appeared to be convalescent. He made an uneventful recovery.

CASE II.

Private P., aged 22, on admission from the detention hospital on January 25th, 1919, said he had felt ill for seven days. His face was flushed and cyanosed, lips deeply cyanosed, conjunctivae injected; he complained of headache and general malaise. Temperature 103°; there was no malarial history. He had vomited several times; was not very clear mentally and was delirious. The pulse was rapid and small, there was definite congestion of both bases, and slight friction in the right axilla. Respirations 28, and very distressed; he was tossing from side to side.

On January 26th there were crepitant râles all over both bases;

cells already ripe in the bone marrow, which respond to what he calls the "chemiotactic whistle."

How many times have all of us said to anxious relations of a patient suffering from acute pneumonia, cyanosed, dyspnoeic, sweating, poisoned, "I can do no more—it is a fight for life between his natural resistance and his disease; if anything can save him it will be nursing; we must wait for the crisis, but his strength is waning"?

I feel that nuclein converts the watching role of the physician into one of active combat, and for me at least it has robbed lobar pneumonia of some of its terrors. Other

conditions exhibiting a leucopenia may respond to similar treatment, and the importance of the role of the phagocyte increases if at will we can increase the strength of the phagocytic phalanx against invading armies of hostile bacteria.

However that may be, I commend to your attention this somewhat unusual method of treatment, and wish to lay emphasis on its importance, because, at the risk of being dubbed an enthusiast or an empiricist, I hold that it is a weapon by which we can with some degree of certainty control

a disease which at times assumes the proportions of a plague amongst us, and is at all times one of the principal contributors to the death rate of any nation.

CONCLUSIONS.

1. That pneumonia is the result of lowered resistance.
2. That lowered resistance is coincident with, if not caused by, leucopenia.
3. That leucopenia is the result of a toxin which temporarily paralyses the power of the system to respond to the chemiotactic call of bacterial invasion.

CHART 1.—Case of right basal pneumonia—toxic, cyanosed. White count before injection of sodium nucleinate, 3,600; after sodium nucleinate, 11,800.

CHART 2.—Case of influenza in a delicate man, aged 37, complicated by pneumonia on the sixth day. Sodium nucleinate on the seventh day; crisis on ninth and tenth days. White count increased by 4,000 in three days.

CHART 3.—Man, aged 26, admitted to hospital on the seventh day of illness: cyanosed, toxic, stuporous, vomiting; both bases pneumonic. On the eighth day seemed moribund; white count, 3,200. Sodium nucleinate given: he improved immediately. Crisis on the eleventh day. White count on the thirteenth day, 17,500.

the sputum was purulent and blood-stained. Sodium nucleinate 0.05 grain was injected hypodermically, and every four hours he was given sodium bicarbonate 1 drachm, ammonium carbonate 5 grains, tincture of squill 7 minims; alternately with the above he was given potassium iodide and creosote emulsion. The day following this treatment there was a marked improvement in the patient's condition: the respirations were easier, the pulse less rapid, and he felt comfortable; cyanosis persisted. On January 28th the temperature was normal, pulse 76. The patient said he felt well. Cyanosis still persisted; basal congestion was well marked. The temperature did not rise again, and the patient has remained well.

Dr. Alfred Piney of Birmingham, in a critical letter to the editor of the *Lancet* (February 4th, 1922), pointed out that his own researches and also those of Muir and Andrews demonstrated that although a marked leucopenia occurs in influenza, yet the bone marrow of cases succumbing to influenza does not demonstrate any definite depletion or exhaustion of the marrow. He says that one is not dealing with an acute aplasia of the bone marrow, and suggests that our method of treatment does not depend upon a direct stimulation of a leucopoiesis as we originally implied, but upon the establishment of a leucocytosis at the expense of

4. That sodium nucleinate, injected intramuscularly, has the power to overcome this disability and to call out the reserves of leucocytes stored in the marrow, converting the leucopenia into a leucocytosis, thereby precipitating the devolution of the disease.

5. That the effect of sodium nucleinate is independent of the duration of the illness, provided the patient is not in a dying condition before it is administered.

6. That the action of this remedy is greatly facilitated by intensive alkalization of the system by the administration of large doses of sodium bicarbonate.

7. That lobar pneumonia reacts more typically and satisfactorily than does bronchopneumonia.

Finally, my thanks are due to all those gentlemen with whom I saw cases in consultation, to Dr. Alfred Piney for his kindly criticism of our original paper, and to my collaborator in Egypt, Dr. J. Graham Willmore.

REFERENCE.

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