A SEARCH FOR AN IDEAL ANTIGEN FOR THERAPEUTIC IMMUNIZATION.

BY

SIR THOMAS HORDER, Bt., M.D.,
PHYSICIAN TO ST. BARTHOLOMEW'S HOSPITAL,

AND

N. S. FERRY, Ph.B., M.D.,
PARKE DAVIS RESEARCH LABORATORIES.

It is now more than twenty years since Wright introduced the principle of therapeutic immunization against various microbic infections by the injection of bacterial vaccines. Wright's discovery gave an enormous impetus to the study of active immunity in microbic diseases. Although at first the range of therapeutic trial of the method of specific inoculation was of necessity much wider than it is to-day, experience has demonstrated that the principle has a much greater value in some infections than in others, and in certain types of disease than in others. It is probable that we do not even yet know the limits of the method, though it is already certain that it has limits, and these of a very definite kind. Especially is its value limited when infections are generalized and when the tissue resistance of the patient is at a low level. In the treatment of such a grave and common disease as acute streptococcal septicaemia, for example, the failure of vaccine therapy is notorious, while in chronic streptococcal endocarditis response to therapeutic inoculation does not occur.

It cannot be said that in specific antisera, at least in the case of the streptococcus again, the practitioner has a remedy which is much more potent than it was twenty years ago. There are those who consider that Besredka made an appreciable advance when he introduced the use of "sensitized vaccines," and certainly this mixed type of bacterial antigen, in combination with specific antibody, appears to be of definite value in the treatment of septicaemic processes when the infection is one for which a homologous antiserum is available.

In spite of the last-mentioned contribution to the subject, however, it cannot be said that the treatment of bacterial infections of the "pyogenic" class has advanced materially during the past decade, and this is true whether we consider the matter from the aspect of bacteriotherapy or of chemotherapy. Sometimes hope swings over to the side of chemical agents, at other times it turns to "specific" measures. Occasionally, since these things have a vogue at present, the physician wonders if physical processes may not possibly hold some more potent means available for the septicaemic patient. In the search for remedies the donor of blood has not been omitted, and various forms of "immuno-transfusion" have been exploited, though so far to very little purpose.

NON-SPECIFIC INOCULATION.

Of late years a great deal of non-specific treatment of infective processes has been carried out by methods which are generically termed "protein shock." The undoubted benefits which have occasionally followed these efforts, the not infrequent improvement following directly upon the use of a bacterial vaccine which later experience of the case proves not to be specifically related to the infection, together with some other pieces of evidence, have led some observers to consider if most of the good results following the employment of bacterial vaccines may not be of the nature of protein shock. This doubt may, however, be read to be as much a measure of disappointment at the meagre results of vaccine therapy as a convincing conception of the mode of its action. For it may well be the fact that it is not so much that bacterial vaccines are not specific as that they are not specific enough. It can scarcely be doubted, in view of all the known facts of natural and of acquired immunity, that in the stimulation of the patient to produce specific antibody there lies, dormant but available, a much larger field of response than has hitherto been entered by the use of any antigen yet placed in the practitioner's hands.

It seems clear that a new method is essential in order to advance from the present position where the treatment of pyogenic infections has paused for so long. Wright's introduction of vaccine therapy gave a great fillip, not only to the treatment of infective processes by specific inoculation, but to the study of antigen therapy in general. It is important to cast about for new remedies of the antigen class, to devise new experiments with this object in view, and especially to maintain an open mind as to possibilities which may have become hidden, as possibilities oftentimes are hidden, by assumptions which have gone before and which, through the course of years, are mistaken for facts.

In this paper it is proposed to give a survey of the various forms of antigen that have been used for the purpose of therapeutic immunization and to describe a new one, with the steps which led up to its discovery and the uses to which it may, in our judgement, be put.

SURVEY OF METHODS OF PREPARING ANTIGENS.

The methods of preparing bacterial antigens for immunizing purposes, proposed from time to time, have been many and diverse. Following the original discovery that suspensions of dead bacteria in a neutral medium, sterilized either by heat or by chemical action, were capable of protecting against bacterial infection, bacterial "vaccines" (Wright) have been used for this purpose almost to the exclusion of other forms of antigen; moreover, these bacterial vaccines have been considered to be a standard by which the immunizing values of other antigens could be measured.

Since the time when vaccines were placed upon a practical basis, however, a good many other antigens have been proposed, and have been actually prepared for purposes of laboratory research. A few of these have also been made available for therapeutic use. None so far has approached very nearly to the ideal antigen, perhaps little closer than did the original bacterial suspensions. The ideal antigen for therapeutic purposes should exist in aqueous solution; it should be protein-free; it should be non-toxic; it should be rich in immunizing properties.

The various methods adopted to prepare antigens for immunizing purposes may be reduced to four, according as the product of the method is (1) a bacterial suspension of a culture grown upon solid media, (2) the whole broth culture of a micro-organism, (3) the filtrate of a broth culture, or (4) an extract of the bacterial cells obtained in various ways. In all of these resultant products the antigen exists in a crude state, adulterated more or less with substances which are not only of no value in the process of immunization, but are not seldom extremely injurious to the patient, as well as to the antigen itself.

Although the exact nature of the antigenic substance is not known, since it has never been obtained in a pure state, it is undoubtedly specific in any particular antigen. In other words, each micro-organism has its homologous antigenic or stimulating substance, and the production of immunity depends upon some sort of favourable interaction between this substance and the cells and tissue fluids of the body. A weak antigen tends to excite the formation of a weak antibody, while a strong antigen stimulates an antibody response more or less proportionate.

In preparing antigens, therefore, whether for experimental or for therapeutic purposes, including the production of antisera, it has been the ultimate aim of all investigators to obtain these substances in a form which might stimulate the highest degree of specific antibody response with the least noticeable reaction on the part of the host. It has long been recognized clinically that severe general reactions, and to a less extent also severe local reactions, tend, in greater or less degree, to lower the resistance, or to diminish the defensive power of the body. This results from the failure of the tissues to respond to their fullest capacity to the stimulation of the antigenic substance, part of their energies being spent in combating substances not in the least concerned with the production of immunity, but harmful to the whole economy. Such relative failure is well illustrated in the attempt to produce immunity to diphtheria by the use of the broth filtrate of a culture of the diphtheria bacillus. This filtrate, which is in effect a solution of the diphtheria toxin, contains

both a poisonous portion, which is non-antigenic (non-immunizing), and an immunizing portion, which is non-toxic. In order to utilize the latter portion of the diphtheria toxin to its fullest extent in practice, the toxic portion is neutralized by the addition of diphtheria antitoxin, giving us the product known as the toxin-antitoxin mixture of Von Behring¹; or it is rendered harmless by exposure to heat or to certain chemicals, leaving the toxoid or immunizing portion available as an antigen, the diphtheria toxoid of Glenny and Hopkins,² or the anatoxin of Ramon.³ With the same object in view Larson,⁴ by the use of soap, also produced a detoxicated diphtheria toxin.

Substances, such as various proteins, innocuous in themselves but prone to be poisonous when injected or absorbed parenterally, are invariably found in association with the antigenic substance in all antigens at present available. Such proteins—originating either from the bacterial bodies or from the media in which the bacteria have been cultivated—always excepting those which are intimately connected with the antigenic substance itself—are considered non-essential to the antigen and more or less harmful. To isolate the antigen proper from these proteins in a pure state has been a problem beset with many difficulties, since all known procedures for ridding the antigen of them have been undertaken only at the expense of weakening the value of the antigenic substance itself.

Seeing that the antigenic substance has been considered to be itself protein in nature, or to be closely associated with the proteins of the bacterial cell, it has been the practice of some workers to prepare extracts of the bacterial elements which should contain as much of the bacterial protein as possible, rather than to utilize the whole bacterial body as a form of antigen. In many instances, and where a special purpose was in mind, this procedure has proved fairly satisfactory.

One of the first and most widely used methods of extraction on these lines was that of Besredka,⁵ who triturated in a mortar a mixture of salt and bacteria dried *in vacuo*. The extraction was carried out by the gradual addition, during trituration, of distilled water until the final content of salt in the solution approached 0.85 per cent. Macfadyen⁷ and others have obtained important results by triturating frozen bacteria by special machinery and extracting with water or with salt solution. Another method turns upon allowing the bacteria to remain in their nutrient fluid media for prolonged periods. This method has disadvantages, in that it not only results in extraction of the proteins from the bacterial cells, but it permits of the retention, in the final product, of the autolysates and poisonous metabolic substances contributed to the media. This method, which was originally employed by Kraus⁶ in the production of his antigen for the precipitin test, is used also in the preparation of some of the tuberculins. Prolonged incubation of a suspension, in normal saline, of live or of dead bacteria, will also produce an extract containing antigenic properties, but the antigenic value of a solution obtained in this manner is weak, and therefore it is of little value. It has been customary for many years to dissolve the bacterial cells in alkaline fluids, such as N/10 sodium hydrate, and from this solution to precipitate the protein. One of the best alkaline solvents for all except acid-fast bacteria was found to be "antiformin." It has been shown by several investigators that by the tryptic digestion of bacteria, as originally suggested by Hirschfelder,⁸ antigen more or less free from extraneous constituents may be obtained.

While these various methods of extracting the proteins or so-called endotoxins from bacterial cells have been successfully applied when the antigen was merely required for certain serological purposes, it was early discovered that antigen obtained in these ways did not fill the role required of it from the clinical standpoint as a substitute for the whole bacterial cells themselves, and therefore other means of attaining the desired end have been sought.

D. Thomson in 1919⁹ described an extract of the gonococcus and other micro-organisms prepared by dissolving the elements in N/10 alkaline solution and precipitating in a weak acid solution. The precipitate, washed and redissolved, resulted in an extract said to be non-toxic in nature and of high antigenic value. Extracts prepared in

this manner have been called "detoxicated vaccines." In 1920 Douglas and Fleming,¹⁰ with a view to rendering bacterial cells more soluble in the body fluids and thereby more readily absorbed for purposes of immunization, extracted the elements with acetone by means of a Soxhlet's apparatus. It was found that the resulting material, in the form of a sterile, dry, white powder, was very soluble in media containing tryptic and other proteolytic ferments. These authors concluded that this type of antigen appeared to possess immunizing properties fully as great as those of vaccines, and also that it formed a very suitable antigen for use in complement fixation tests. Jenkins,¹¹ in 1921, by modifying the preparation of "detoxicated vaccines" as described by Thomson, and incorporating a method of detoxication described by Dean,¹² produced what he termed "residual vaccines." Dean had previously used hydrogen peroxide as a detoxicating agent in the preparation of various vaccines, especially of dysentery bacillus vaccine, and claimed that they were rendered non-toxic thereby. In 1923 Dreyer¹³ gave us "defatted vaccines," later called "diaplyte" vaccines and antigens, and claimed that it was possible to obtain better results with the use of antigens freed from surrounding fatty or lipoidal material than with those prepared in any other way. While this work of Dreyer, as also that of Douglas and Fleming before him, appeared to lead to conclusions diametrically opposed to those following the researches of others, especially of Warden,¹⁴ who held that bacterial antigen is lipoid in character, it is interesting in that it would, on the surface, seem to prove that the specific antigenic substance may be obtained from different parts of the bacterial cell and by different methods.

THE NATURE OF THE ANTIGENIC SUBSTANCE.

During the past two or three years several investigators, and especially Heidelberger,¹⁵ Zinsser,¹⁶ Perlzwig,¹⁷ and their associates, have been carrying out some extensive experiments in an attempt to throw more light on the character of the antigenic substance, and considerable progress has been made. Most of this work has been done with the pneumococcus, and certainly suggests that the possibilities of obtaining a protein-free antigen are by no means hopeless. In the course of these researches a soluble and highly specific substance was purified and concentrated from the three types of the pneumococcus by Dochez, Avery, Heidelberger, and others. This was obtained free from nitrogen, and appeared to be of a polysaccharid nature. This substance, however, is non-antigenic, while the protein substance is antigenic. Perlzwig, Steffen, and others isolated an antigen from the three types of the pneumococcus by prolonged tryptic digestion and extraction of the digest with 70 to 80 per cent. alcohol. This antigen is insoluble both in absolute alcohol and in ether, and in all lipoidal solvents. It is not impaired by boiling for five minutes nor by heating at 56° C. for one hour. It would appear from these researches that bacterial antigenic substance is, in the case of the pneumococcus at any rate, of the nature of a lipid, and that it probably adheres to the protein fraction of the cell in loose union.

A NEW TYPE OF ANTIGEN.

The work now to be summarized was begun in 1921 by Ferry and was continued by Ferry and Fisher. Many details of these researches have been already published.^{18, 19} The experiments had for their purpose the determination of the practical value, from an immunizing standpoint, of bacterial antigens prepared after various methods. They were originally undertaken as the direct result of suggestions made by Horder. In carrying out the work a large number of antigens prepared from several different micro-organisms were tested, in the hope that a substance would be found fulfilling more satisfactorily than any in present use the requirements of an ideal antigen.

The work was first undertaken with broth cultures of the typhoid bacillus, colon bacillus, pneumococcus, and other bacteria of the (so-called) endotoxin-producing class. It was found that the antigenic properties of the filtrate were higher than anticipated, having regard to previous conceptions of the antigenic properties of broth filtrates

generally in this class of bacteria. It was also found that these properties varied more or less inversely with the time of incubation of the cultures. In other words, the shorter the incubation time, within certain limits, the higher the antigenic titre of the filtrate, the optimum incubation time being from eighteen to twenty-four hours. Filtrates from cultures incubated for five and ten days were very low in antigenic power. This experiment was carried out several times with similar results, leading to certain deductions which were contrary to ideas previously held. Reasoning from past experience with diphtheria and tetanus toxins and with toxins of similar nature to these, it was concluded, in the first place, that the antigenic substance pertaining to the class of bacteria under observation is probably not of the extracellular type, because if it were it would probably have been stronger at the end of several days than at the end of eighteen or twenty-four hours. It was concluded, in the second place, that if the antigenic substance were of the endotoxic variety, strictly so called, it would again have been found stronger after several days' incubation than after the early stages, since more of the antigenic substance would have been dissolved out of the cells and have been evident in the filtrate. It would seem, therefore, that this stimulating substance which we term antigenic substance must be more or less loosely bound up with the bacterial cell and is to be found in the broth as a washing from the bacterial surface or ectoplasm rather than as an extract from the endoplasm of the cell.

As a result of these observations with broth filtrates it was argued that, if the antigenic substance could be so easily washed off the bacterial cells and was to be found in the broth as early as eighteen hours after planting, it ought to be obtained, and in a higher degree of purity, in the washings of bacteria grown on solid media. In order to prove this point some preliminary tests were carried out with the typhoid bacillus. This micro-organism was chosen because it grows very readily on ordinary media and because the antigenic properties of the particular strain of typhoid bacillus in use were more or less known to us. In carrying out these experiments twenty-four-hour agar growths were washed off with normal saline and the suspensions of bacilli were immediately agitated for a few minutes in a mechanical shaker more quickly to yield a homogeneous suspension and to facilitate the extraction of the antigenic substance. In order to clarify the suspension of bacilli with as little loss of antigenic properties as possible, it was passed through a Sharples centrifuge in place of a porcelain filter, for it had been found earlier in the work that if the washings were passed through porcelain filters they lost, probably by absorption, more or less of their antigenic power: for this reason clarification by means of the centrifuge was here adopted. These washings, when received from the centrifuge, proved, as anticipated, to be highly antigenic, even more highly than the broth filtrates, and in some instances more highly than the suspensions of bacilli from which the washings were obtained. The washed bacilli were, in every instance, very low in antigenic content, showing that the mere washing had taken from them a large part of their immunizing power.

In carrying out the experiments with the broth cultures and the cultures grown on solid media all operations were done as quantitatively as possible. Twenty-four hour broth cultures or salt suspensions of the bacilli, grown for the same length of time on the solid media, were divided into three parts: one part or fraction to be tested as a whole; one part to be centrifuged for the preparation of the filtrate fraction, which we called the "centrifugate"; and one fraction to be centrifugized for the sediment. This last fraction was diluted to the original volume with normal salt solution. These fractions were sterilized by the addition of 0.3 per cent. cresol instead of heat, as experience had shown that heat is injurious to antigen, especially to the immunizing portion of it. The antigenic or immunizing properties of these fractions were determined by injecting them intravenously into rabbits of equal weight in the same number of doses, usually four, and testing their serums, according to various serological methods, for antibody content.

Washings from other bacteria also supposed to be of the endotoxic variety, such as the colon bacillus, pertussis bacillus, streptococcus, gonococcus, and especially the pneumococcus,²⁰ were prepared and tested as above, and antigens of extremely high value were obtained. These results corroborated the work on the typhoid bacillus, and confirmed the deduction that the antigens of this type of micro-organism are very loosely bound to the bacteria, and that it is not necessary to break up the bacterial cell in order to liberate the antigenic material.

The fact that the bacterial cells were intact and, so far as the eye could discern, were not broken up, was shown by means of staining and observing under the microscope, and also by plating, a comparison being made between the number of colonies obtained and the number of bacteria in the original suspension.

"ECTOANTIGEN."

A very important point was brought out at this time—to wit, the fact that washing the organisms in this way extracted the antigenic substance from the bacteria, while the toxic principles were left behind. Tests showed that the washings were non-toxic, while the washed bacterial cells were practically as toxic as before, as they produced reactions similar to the unwashed cells. The toxins or poisonous substances retained in the bacterial cells, therefore, are apparently endotoxic in nature, while the antigens are seemingly derived in great part from the ectoplasm. The antigens in question, therefore, are in all probability not identical with the endotoxins or endopoisins, as has been taught, but appear to be entirely different substances. As it would appear from these results, and others which Ferry and Fisher have reported, that the antigenic or immunizing portion of the bacterial cell is more ectoplasmic than endoplasmic in origin, it is proposed to call this type of antigen an "ectoantigen," and for products prepared in such a manner as to contain only this ectoantigen the designation "immunogens" is suggested, to distinguish them from other antigenic products already in use.

A further study of this type of antigen elicited several other facts of extreme interest. One of the first experiments in the attempt to produce an antigen of superior value was carried out by treating broth cultures with sodium hydroxide, as this chemical had been used for a number of years by many investigators for the disintegration of bacteria, in the belief that by destroying the bacteria the endotoxin or antigenic substance is set free. The results, however, were disappointing in that the antigenic properties were found to be more active in the original broth cultures and in the broth filtrates from the original culture than in the material remaining after the sodium hydroxide had been allowed to act. There was no doubt about the fact that the bacteria were broken up and the contents set free, but the liberation of the so-called endotoxin in no way increased the antigenic properties of the filtrates. On the other hand, something, probably the alkali, had a very injurious effect upon the antigen, since the broth culture and its filtrate stimulated rabbits to produce agglutinins of the titre of 1 in 16,000 and 1 in 10,000 respectively, while the fractions acted upon by the alkali only stimulated agglutinins of titres as low as 1 in 150 and 1 in 2,000. Somewhat similar experiments were next carried out, using antiformin instead of sodium hydroxide, and the results were practically the same. The immunizing value of the antigen was nearly destroyed during the process of extraction.

TITRES OF BACTERIAL WASHINGS.

Another experiment was undertaken to show the relative values of bacterial autolysates, artificial aggressins, and bacterial washings ("immunogens"), as it was felt by some that these three products must be closely related. The results, however, were very convincing of the fact that they were not at all alike. Serum resulting from the injection of the agar washings gave an agglutination titre of 1 in 12,000 and a complement fixation titre of 1 in 750, while the aggressins gave titres of 1 in 5,000 and 1 in 500 respectively. The autolysate from the residue of the agar washings gave titres of 1 in 3,000 and 1 in 100, while that

from the residue of the broth filtrate titred 1 in 5,000 and 1 in 500. An autolysate from an agar culture not previously manipulated in any way gave an agglutination titre of 1 in 7,000. We have concluded from these results that autolysates and aggressins are antigenic, not because of the lysis of the bacteria or of the extraction of the antigen by shaking and long standing, but because they contained some of the antigen which had been washed from the exterior of the bacterial cell and which had lost some of its antigenic properties as a result of the method of treatment. The more of the antigen that is previously washed off the cell, the lower will be the titre of the serum stimulated by the sediment left by lysis or the autolysate from the sediment, whether washed or unwashed.

Nitrogen determinations of these bacterial washings show that the total nitrogen in them is very much lower than in that of any other bacterial antigens at present in use, including such well known antigens as bacterial vaccines, glycerinated vaccines, detoxicated vaccines, and serobacterins. The fact that the washings were low in nitrogen content and high in antigenic properties led to experiments to determine, if possible, if washings rendered protein-free would show any immunizing properties. Three methods of precipitating the protein were followed, including the use of acetone, phospho-tungstic acid, and uranium acetate. In the first method the acetone was removed by evaporation under vacuum in order to use as little heat as possible, and in the third method the solution was freed from uranium by precipitation with sodium phosphate. Agar washings of *B. typhosus*, *B. coli*, pneumococcus, streptococcus, and gonococcus apparently protein-free were found to stimulate antibodies of appreciable value, as shown by agglutination and complement fixation tests.

As a final experimental procedure tests were carried out on animals in order to compare these washings with therapeutic antigens prepared after various other methods. The results in every instance were favourable to the washings. In carrying out these tests rabbits were given three intravenous injections each of the antigens, diluted to contain the same number of micro-organisms per cubic centimetre, or their equivalent in antigen, and bleedings were made seven days after the last injection. The serums from these rabbits were then tested for antibody content, according to several well known serological methods, and the results tabulated. As stated above, the antigenic properties of the washings per cubic centimetre, estimated on a quantitative basis, exceeded those of any of the other antigens tested.

It was concluded, therefore, as a result of these last tests and others previously carried out, that these washings more nearly approached the ideal antigen than any which had come under the observation of the writers. This last statement is based on the fact that these washings are in aqueous solution, are low in protein content, are high in antigenic properties, and are practically non-toxic.

CLINICAL RESULTS AND DOSAGE.

Following the experimental work on these "immunogens" steps were next taken to test them on a practical basis. They were sent to a considerable number of clinicians, choosing those who had suitable cases in their clinics, and who were known to be conversant with, and able to give time and attention to, systemic observations of their patients throughout the treatment. While the first trials were carried out more or less as a preliminary measure in order to determine the safety of the remedies, the results justified the procedure, and a more extensive trial was then attempted. The subcutaneous, intravenous, and intramuscular routes for injection of the antigen were compared. So also were various intervals of time in the course of different disease processes. Altogether these trials have been pursued over a period of two years. The intramuscular route appears to be the one of election, and daily injections appear to give the best results. These conclusions are, however, only tentative, since the experience of different observers varies, and the best mode and the interval of injection doubtless depend upon the type of the disease, whether acute or chronic, general or local.

It has been found by a series of trials that the most useful concentration of the antigen is one which allows of

an initial dose of 0.5 c.cm., with increments rising to 2 c.cm., and, on occasion, to 5 c.cm.

It is as yet too early to speak of the main results of the use of this antigen, still less of statistical results. To quote concrete cases, however successful they appear to have been, can avail little, although it is hoped to do this later when a larger number have been collected. Already, it may be said, however, this form of antigen has become the favourite one in the hands of a good many practitioners who have had experience of various types of these remedies. Promising reports are forthcoming in connexion with streptococcal, pneumococcal, and gonococcal infections especially. That reactions of an undesirable kind are absent after injection of this antigen is a fact recorded by almost all those who have used it, and this clinical observation confirms the results of its experimental use in the laboratory.

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SYMPTOMS, PATHOGENY, DIAGNOSIS, AND TREATMENT OF ADDISONIAN ANAEMIA.*

BY

A. T. TODD, M.B., M.R.C.P.,

ASSISTANT PHYSICIAN, BRISTOL ROYAL INFIRMARY; DEMONSTRATOR
OF PATHOLOGY, UNIVERSITY OF BRISTOL.

THIS disease is worthy of consideration on account of its frequency—I have been meeting with one case a month for the last two years—and because of the mistaken diagnoses which have been made: neurasthenia, neuritis, chronic rheumatism, pelvic pressure neuritis, food poisoning, colitis, and carcinoma of the liver have been some of the diagnoses in this series—tragic mistakes, for the disease appears to be amenable to treatment if only the diagnosis is made early.

SYMPTOMS.

Symptoms are often few and vague, and in a series the presenting symptom shows much variability; tiredness or weakness and the symptoms of anaemia are the most common. Dyspepsia is often met with, but pain is usually slight and vomiting rare. Diarrhoea alternating with periods of constipation is a symptom of importance, and is found in about 50 per cent.; it precedes the anaemia by years, and, as the patient has always had it, information about it is not volunteered. It is severe at times and diagnosed as colitis; in one case a severe attack following a meal of suspected fish led me to diagnose food poisoning for two weeks. Premature greyness occurs in a large number of the cases. Glossitis, another symptom which precedes the anaemia, is common; painful cracks and fissures occur for years, and each patch heals slowly, leaving behind it atrophied epithelium devoid of papillae. These atrophic patches spread gradually over a large part of the tongue, and produce the smooth glazed tongue of the declared condition. This glossitis appears to be the sequel of suppurative periodontitis, past or present, and it is found apart from the disease under discussion, though rarely to the same degree. In the less marked cases the glossitis may be unmasked by swabbing the tongue over with dilute acetic acid.

Nervous symptoms, usually those of subacute combined degeneration, are frequent in the later stages of the disease, but symptoms of this condition were the presenting complaints in a third of the series. Abnormal sensations, due to degeneration of the sensory tracts or nerves, are the first and are very misleading, for there is no loss except of deep sensation; the vibration sense, fortunately one of the easiest to test, is one of the first to disappear. As the sensory changes are modified qualitatively, rather than

* A paper read before the Bath and Bristol Branch of the British Medical Association.