

THE ÆTIOLOGY OF THE CONFUSIONAL SYNDROME AND THE USE OF T.A.B. VACCINE.*

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SINCE the discovery that *Bacillus coli* vaccine (1) or albumose (2) were as effective as typhoid vaccine (3) in the treatment of typhoid fever, the use of non-specific protein therapy has been popular for almost any disease for which there is no other satisfactory form of treatment. T.A.B. vaccine, a mixture of typhoid and paratyphoid A and B organisms, has been found more regular and reliable in its results than typhoid vaccine (4); but milk, antitoxic sera, peptone and a variety of other substances have been used, and even malaria is considered a form of this treatment, segmentation of the parasites producing the foreign protein (5). It has been observed that Gram-negative organisms, such as the gonococcus and typhoid bacillus, produce more marked reactions when given intravenously than the Gram-positive organisms, such as staphylococci, streptococci and pneumococci (5).

The treatment has been used extensively for a great variety of skin conditions (6, 7, 8), for eye diseases (9, 10), septic processes (11, 12, 13), arthritis (14, 15), especially if acute (16), and for the more acute manifestations of rheumatoid arthritis (17), for syphilis (8, 18), typhoid fever (19), undulant fever (20, 21), pneumonia (22), tuberculosis (23), asthma and hay-fever (24), chorea (25, 26, 4), epilepsy (28), multiple sclerosis (29, 30), general paralysis and neurosyphilis (31, 32, 33), schizophrenia (34, 35) and for numerous other psychoses (36, 37), for the relief of spasm in vascular diseases (38), and for other purposes too numerous to mention (39, 40, etc.); and it is, perhaps, unfortunate that most of these conditions are characterized by natural improvements or remissions which make the estimation of the value of treatment very difficult. In the field of general medicine the effectiveness of this therapy is fairly well established in certain acute and subacute conditions (41), but its work in chronic conditions is not well substantiated (5). Poor results have been recorded in some organic brain conditions, and the opinion expressed that the treatment is not indicated when these organic changes are present (25).

In psychiatry, T.A.B. vaccine has been used in three chief types of illness.

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It was used for general paralysis before malaria (42) and many still think it is as good as malaria (43, 44, 45). High temperatures are usually aimed at, and produced every second day or according to the patient's condition (46, 33).

Secondly, it has been used as a form of shock therapy for various endogenous psychoses; high temperatures and severe reactions are produced on the assumption that the shock itself initiates a resynthesis of mental processes, or that the severe reaction increases the patient's resistance to occult forms of bacterial infection. Thus one of my patients, a young female schizophrenic in good physical health, was given 10 million bacilli intravenously as a preliminary test dose, and a few days later received 500 million intravenously. The temperature began to rise in half-an-hour, and, following a severe rigor and repeated vomiting, the temperature reached 105° F. in three hours, a total rise of 8° F. following the injection, the respiratory rate increased to 32 and the pulse-rate was about 140, with periods when it became so rapid and thready as to be uncountable. Tepid sponging was necessary at intervals during the next two hours, when the temperature fell to 103° F., and it was still above 100° F. eighteen hours after the injection. The total duration of the pyrexia was fifty-four hours. There was a clearing of the mental symptoms for a few days after this as striking as anything I have seen after one hypoglycæmic shock, but it could not be tolerated with the frequency that one can give insulin shocks.

It is with the use of T.A.B. vaccine in the third type of mental illness that this paper is chiefly concerned, and I do not propose to discuss the treatment of general paralysis or shock therapy again.

This type of illness includes all cases where what one may call the confusional syndrome is present, sometimes in a pure form, but very often associated, if symptomatology counts for anything, with one or other of the endogenous psychoses. The mental symptoms of this syndrome are varying degrees of confusion with disorientation, restlessness without apparent purpose, memory disorders, perplexity, apprehension, and so on, and there are usually a variety of physical signs associated with them. The skin, especially of the face, may be greasy, sallow or blotchy, or studded with septic spots, the nails may be brittle or lined, the hair dry, and vasomotor disturbances are common, flushing, pallor, dermatographia, with a variable temperature, which may be subnormal or slightly raised, and a pulse-rate which is fluctuating, generally increased and sometimes irregular. A dirty mouth, cracked, dry lips, poor appetite and bowel disturbances are frequent and red cells and hæmoglobin may be diminished, with a variable white cell-count showing a general tendency to increased numbers, especially of immature polymorphonuclears. The urine frequently contains albumen and acetone, tendon reflexes are often exaggerated and the pupils dilated. Frank sepsis in teeth, tonsils or sinuses may be present, but in my experience they are almost as frequently found where the confusional syndrome is absent.

DOSAGE OF T.A.B. VACCINE.

In treating this type of illness with T.A.B. vaccine I am careful to avoid severe reactions. The reaction depends on the patient and not on the dose ; 5,000 million bacilli have been given intravenously without ill-effect (47), and a series of fifty-seven injections has been given without harm (48), but severe reactions have been produced as often with small doses as with large ones (49), and this is because the effect of T.A.B. is most marked with the first dose, and because one usually starts with a small dose. It is generally agreed that the more chronic the illness the less is the reaction to T.A.B. vaccine, and I believe this to be suggestive evidence against the view that the confusion in the cases we are considering is due to chronic sepsis, for the reaction in many of these cases is very sharp, even to small doses. I shall return to this later.

The first dose should be small ; in cases where the toxæmic symptoms are marked, as small as one or two million. I use Burroughs Wellcome T.A.B. vaccine, which has 1,000 million typhoid bacilli and 750 million each of paratyphoid A and B in each c.c., these numbers being a reasonable approximation, and I calculate all doses on the basis of the typhoid bacilli only ; a dose of two million would thus be one of five million bacilli. This is for convenience only. In general the injections are tolerated less well as age advances. Arndt (50) states that weak stimuli accelerate vital activities, but strong stimuli inhibit them and maximal stimuli suppress or destroy them, and this is an excellent principle to adopt in practice. If the dosage is too great the patient may become progressively worse with each injection (51, 52). The injections can be given daily, weekly, or at any interval between. At Hatton we usually give them twice a week. The dose is increased as required, a temperature of something less than 102° F. being aimed at.

THE ORDINARY REACTION AND THE T.A.B. INDEX.

Following a prodromal phase of about half an hour, a chill or rigor is followed by a rise of temperature, which reaches a maximum in two to five hours. This rise is accompanied by aching, discomfort, nausea and irritability, and resembles the onset of an acute infection. Inflammatory foci are said to become more painful. This reaction is often referred to as the negative phase. An attempt has been made to avoid much of the unpleasantness of this reaction by the use of the typhoid flagellar or H antigen (53), which is said to be just as effective (33), giving a longer lasting and higher temperature, but less sickness and headache.

The second or positive phase represents the defervescence, which is usually rapid, but may be prolonged in first reactions. The patient feels better and is often slightly euphoric (49, 5).

In estimating the effect of an injection, besides the clinical appearances I

use a T.A.B. index, which is calculated by multiplying the highest rise in temperature above the temperature when the injection was given, by the duration of fever and dividing by the dose used. The temperature, T , is obtained by measuring the rise in one-tenths of a degree Fahrenheit, the duration, D , is the time in hours, and the dose, V , is the number of millions of typhoid bacilli only injected. Thus, if the temperature rose from 97° to 101° , the fever lasted 20 hours, and the dose was 5 million, the index would be $\frac{40 \times 20}{5} = 160$. In

12 non-confusional psychotics the average readings of this index for 6 successive injections were 46, 22, 9, 4, 2, 1. The average rise of temperature was 4° , giving an average temperature of 101.2° , and the duration varied from 10-20 hours. The chief exception to this average picture is that occasionally in non-confusionals the first index is higher. The dosage reached in six injections might be 500 or even 1,000 million.

One of the 12 non-confusional cases referred to had pus in the right antrum and septic tonsils, both of which were treated by operation, but although T.A.B. treatment was given before the operation, no special reactions were noted. In the 12 cases the temperature reached a peak between three and five hours after the injection and then began to fall, reaching a low level, which was something higher than that before the injection after about seven to nine hours, and then a further rise took place, giving a second peak at ten to fourteen hours. Apart from very occasional exceptions the second peak flattens out or disappears after the second injection.

In 12 psychotics showing the confusional syndrome, but with no detectable disease that I could label, the average T.A.B. index for ten successive injections was 240, 192, 69, 55, 36, 15, 10, 3, 2, 1. In these cases the first index was rarely below 150, whereas in non-confusional cases it was rarely above 70. In these cases the second temperature peak persisted after the second injection, and was not flattened out until the fourth, fifth or sixth. Often in the early injections there were more than two temperature peaks, and I have seen a case with six distinct peaks spread over three days, ignoring the slight fluctuations which often occur. This type of reaction is to be avoided when possible.

Signs of a too severe reaction are second peaks higher than the first, a persistence of the second peak in many reactions, delay in the development of the peak temperature, and a failure of the T.A.B. index to fall. This latter phenomenon is commonest when a confusional psychotic gives a low first index, and great care is necessary in treatment.

Thus one patient gave a series of indices as follows: 38, 19, 25, 19, 20, 23, 13, 10; and another with the first seven injections gave 72, 24, 57, 46, 68, 52 and 21. The first three were in response to a dose of 5 million, and the next four to a dose of 10 million. At the eighth injection 15 million were given; the patient developed a high and persisting temperature with marked

exhaustion, and died thirty hours after the injection. This is the only death I have seen in connection with T.A.B. treatment in 400 cases. A third patient had an index of 112 with 1 million, 113 with 2 million, and was then given 10 million, which produced a prolonged pyrexia of several days' duration and a general picture of serious illness. It seems that in these cases there is a failure of vital mechanisms to respond to stimulation and produce antibodies, and I shall discuss this again later.

A great deal of attention has been paid to changes in the blood that follow intravenous injections of T.A.B. vaccine (54, etc.), and these blood changes have been found to be very similar whatever antigen is used (15).

The polymorphonuclear leucocytes first fall, then rise to two or three times their original level (27, 5), immature white cells increase from the beginning, and there is a progressive shift to the left of the Arneith index (55). As a rule the picture is again normal in twenty-four hours. The lymphocytes show a slight increase during the first hour and then fall, but their fluctuations are not nearly so marked as in the polymorphonuclears. Eosinophiles usually diminish during the reaction, but occasionally increase, and in two of my patients such an increase of eosinophiles has developed when the ordinary polymorphonuclear leucocytosis was poorly marked. When the expected leucocytosis fails to develop it is a danger-signal, and injudicious treatment may lower the white cell count for a long period (56). The interpretation of white cell counts is difficult because of the wide variations met with in health. There is said to be an increase of young and atypical erythrocytes during the reaction (8, 55), and a general tendency during a course of treatment to an increase in the number of erythrocytes (46).

There is a drop in the clotting level of blood of 50% for twenty-four hours or longer (57); the sedimentation-rate rises during treatment, falling to the original level in seven to thirty days (25); there is an increase of fibrinogen, globulin, thrombokinase, sugar, non-protein nitrogen, proteolytic ferments, antibodies, cell membrane and capillary permeability—in fact changes in every constituent and property of blood have been recorded (8, 49). I have made serial blood urea estimations in 10 patients, and in 6 of these there was little or no change. In the remaining 4 the blood-urea was elevated from 4 to 18 mgrm. %, reaching a maximum in six to ten hours.

Hench (49) considered that there was no definite burden on the kidneys during treatment. Commonly there is a reduction of urine, followed by a diuresis, but this is subject to some variation (58). The excretion of phenol-sulphonaphthalein is sometimes reduced by 50% during the reaction, but promptly returns to normal. Hench (49) suggests a vascular basis for this.

The blood-pressure during the reaction has been variously reported as rising and then falling (5), falling throughout, but especially in the second phase, when the temperature is falling (49), and as only rising in the second phase (55). As a rule, in my cases the systolic blood-pressure rose during the first

few hours and later fell below normal, and the diastolic showed a slight fall from the beginning. Both were normal next day.

THE UNUSUAL AND THE FOCAL REACTION.

Reactions of unusual severity, accompanied by various complications or focal reactions, have been carefully described by Hench (49). They have been divided into four groups :

(1) Stimulation of an infective inflammatory focus in a joint, the eyes, teeth, gall-bladder, appendix, lymph-glands and so on, which may be known or unsuspected. Attempts have been made to use this reaction as a diagnostic test in gonorrhœa and prostatitis (59, 60), and it is a valuable sign when it occurs.

(2) Stimulation of a non-infective inflammatory focus at the site of a fracture or other injury.

(3) Stimulation of latent diathetic phenomena, such as asthma, gout, epilepsy, tabetic crises and delirium tremens.

(4) The development of severe vasomotor or intravascular clinical changes, such as acute vascular thrombosis, anuria, glaucoma. Attempts have been made to explain these phenomena on the basis of allergy or anaphylaxis (61, 62, 63), but the evidence is against this view (64), and Hench (49) found no evidence of it and no previous history suggesting allergy.

Such reactions are very rare, only twenty being reported in 14 patients in a series of 10,000 injections given to 2,500 patients. In 8 of these the reaction occurred with the first dose, which is usually the most severe in its effects (41, 65).

The first of these four groups, where stimulation of an infective inflammatory focus produces an increased exudation of fluid with heightened pain and tenderness, is of interest because of the suggested relation of infective foci to mental disorders. If the stimulation of the focus leads to too great a digestion of inflammatory tissue, it is suggested that systemic auto-intoxication follows (49) and the patient is worse, whereas if it is not so severe, a reverse phenomenon reduces the inflammation below the original level. Graves (66) states that if the focus is open, improvement follows, but if closed the patient becomes worse, and he has seen reactivation so acute that discharges have become hæmorrhagic. Since these reactions are so rare it must be largely a matter of chance whether one meets them or not, and I have never seen a focal reaction in 3,000 injections in 400 patients. This means very little unless one is expecting an unusual number of focal phenomena in the confusional psychotics under treatment. The only severe reactions I have seen have been in the nature of systemic collapse, with high temperature, rapid pulse, pallor and greyness of the skin.

ÆTIOLOGY OF THE CONFUSIONAL SYNDROME.

Before discussing the mechanism of action of T.A.B. vaccine it will be advantageous to inquire into what is known of the ætiology of the confusional syndrome. There are many cases where obvious organic disease provides a satisfactory explanation of the mental symptoms, such diseases as uræmia (71, 72), failing heart, pellagra (73), pernicious anæmia (74), puerperal infection, septicæmia, severe head injury and so on, and with these the use of T.A.B. vaccine is of little account.

It is with cases exhibiting the confusional syndrome without obvious reason that I am really concerned. Devine (67) has pointed out that a typical confusional psychosis can arise from purely psychogenic causes, and in a case I observed (68) an exhaustive search for possible factors apart from psychic shock was negative, and the only abnormalities discovered were a delayed return of the blood-sugar level to normal following glucose (69), and a poor response to the water excretion test (70), both of which are found in states of emotional tension. Devine also mentions as causative factors, overwork, domestic, professional, economic and social stress, with worry, fear and anxiety, while other confusions follow mild attacks of influenza which are not taken seriously, or some other infective illness which has apparently cleared completely before the mental illness developed and has left no trace when the patient is admitted to a mental hospital. One can add to such cases a group showing the confusional syndrome, where a careful history reveals nothing that one can particularize except the development of a mental illness. On examining this group of cases which exhibit the confusional syndrome, after excluding the cases of uræmia, severe anæmia and so on, one finds that the great majority of them have certain symptoms highly suggestive of an endogenous psychosis, and often this suggestion is made certain by a clearing of the confusion, when the essential psychotic manifestations are revealed. I am suggesting, therefore, that not only can psychological causes lead to the development of the confusional syndrome, but that this syndrome usually has its origin in a purely mental illness. Devine suggests that psychological tension leads to insomnia, and that loss of sleep allows toxic products to accumulate. Experiment has shown that the effects of loss of sleep are not ordinarily serious when the loss is a voluntary one, but Devine states that this is quite different from loss of sleep due to fear or worry. This may be so, but it brings us back to where we started, that psychological stress can produce the confusional syndrome.

This conception of the confusional syndrome following the onset of the mental illness could be explained in at least two ways. It may be occasioned by some peculiarity of the underlying mental illness, or the mental illness may make the patient more vulnerable to some toxic process already present, which may be chemical or bacteriological in origin. Before proceeding

further with the argument I will discuss the mechanism of action of T.A.B. vaccine.

MECHANISM OF ACTION OF T.A.B. VACCINE.

The reaction produced by T.A.B. vaccine—and for the moment it does not matter if the reaction is a good one or a bad one—is either due to the action of the whole organisms, or to various protein constituents of the organisms. Pickworth (75) found that about 25% of chronic patients, and the same percentage of recent admissions to mental hospitals, were positive agglutinators to pathogenic organisms of the coli-typhoid group and he thought this evidence suggested a causal relationship, and indicated past or chronic infection. He drew attention at the same time to the many factors that affect agglutination, and quoted Ritchie (76), who found a higher percentage of coli-typhoid agglutinators among normal people than Pickworth had found among the insane. The response to T.A.B. vaccine in Pickworth's positive agglutinators was very variable. This tends to indicate that the action of T.A.B. vaccine does not depend on the particular organisms injected, and this conclusion is strengthened when one recalls the very wide variety of pathogenic organisms that have been stated to cause mental illness. However one may juggle with heterologous agglutination, the group phase of H antigens and the common R antigens, one cannot make the scope wide enough. Moreover, specific reactions and results are not observed, and the same effects produced by T.A.B. vaccine can be produced by other antigens. It can be agreed, therefore, that if the action is anti-bacterial, it acts by a process of non-specific stimulation of the immunogenic system (8, 50), even if certain specific antibodies are developed (5, 77). Phagocytosis associated with increased white cells might be important (27), but the leucocytosis is very variable, and very few claim that good results bear any relation to the white cell counts. There is reasonable evidence that non-specific antigens do increase the bactericidal qualities of blood (8, 78, 79), and probably any febrile reaction develops or mobilizes more circulating antibodies. This stimulation of the body defences against bacterial effects is usually accepted as the rationale for the use of non-specific protein therapy in psychoses, the pathogenic bacteria or their toxins being derived from a chronic septic focus.

Returning to the confusional syndrome, one can now examine the possibility that the confusion develops because of the presence of septic foci in the body. The first question that arises is whether septic foci are at all common, and there is a wide divergence of opinion concerning the frequency with which they are found (36, 80, 81), and a similar divergence of opinion about the effects of the removal of septic foci (82, 83, 84, 85). There is a general agreement, on the other hand, that if a septic focus is present it is a chronic one, producing few acute effects, and these very rarely, and so latent that searching operative interference is often necessary to find it. I have described cases earlier in this paper where the T.A.B. index remained rather high with successive injections,

and where the formation of antibodies was defective. Even in these cases the septic focus remains hidden, and the bacteria do not take advantage of the reduced resistance. Any good results obtained with T.A.B. vaccine in the treatment of such foci would be contrary to the majority of opinions in other branches of medicine, where acute and subacute conditions do best (5, 25). In the majority of cases the reaction to the artificial acute invasion with organisms is more acute than is normally found, and the T.A.B. index falls rapidly, showing a satisfactory antibody response. In 1936 I reviewed the treatment and progress of 20 cases of mania admitted to the Hatton Mental Hospital in 1931, 1932 and 1933 (86). They were all the cases of mania admitted on the female side in a series of 410 successive admissions.

They were divided into two groups—7 cases of pure mania and 13 cases of mania with the confusional syndrome. Of the 7 pure cases, 6 recovered after an average stay in the hospital of fourteen months, and the other is still a chronic patient. Of the 13 cases with confusion added, 1 died, and the remaining 12 were discharged recovered after an average stay in hospital of four months. Septic foci were certainly not causal in the 7 pure manias, who were examined and treated very carefully with this end in view. If septic foci were responsible for the confusion in the other group, then we are left with the conclusion that the most severe psychoses develop without septic foci, which only reveal their effects in the milder manic attacks. I have often supposed that the pure manias were so severely affected that no toxic focus was necessary to precipitate a mental breakdown, and that the manic cases with confusion were those not so severely affected, but who succumbed to the added strain of toxæmia. Such a conception presupposes that the toxæmia is an adverse factor, and, followed to its logical conclusion, that one can divide manic cases into four rough groups: firstly mild cases without toxæmia not admitted to hospital, secondly mild cases with toxæmia, thirdly severe cases without toxæmia, and lastly severe cases with toxæmia. The first three of these we know, but I submit that cases of undoubted mania with confusion that form a worse prognostic group than the pure manias do not exist.

The same relationship is observed in schizophrenia; when the disease is present in a clear sensorium the prognosis is much worse. In addition to this the relative absence of focal reactions during treatment with T.A.B. vaccine is also against focal sepsis as a causal agent.

I suggest, therefore, that the development of confusion in these cases is a peculiarity of the underlying mental illness, and I suggest that this development is bound up with the fact that the mental illness has a better prognosis, and is not so severe as when confusion is absent. The confusion could arise because of a longer preservation of insight, and the stress and exhaustion associated with the attempt to hold on to reality.

The physical changes would be secondary to central disturbances arising from abnormal nervous mechanisms or the development of chemical toxins.

Whatever the ultimate pathology, I believe that T.A.B. vaccine, used to produce moderate or mild reactions, will help to shorten the course of this confusional syndrome in many cases, leaving a mental illness so mild that apparent recovery of mental health soon follows. The treatment is empirical, and if it is antibacterial in any cases it is because the infection is subacute and not chronic, dependent on metabolic or other disturbances which are centrally conditioned. There is a variety of effects of T.A.B. vaccine that may possibly be involved; thus it has been suggested that it acts through the autonomic nervous system, the clinical phenomena being described in terms of alternating sympathetic and parasympathetic dominance (55, 87, 88, 89); also that results can best be considered as following a general increase of basal metabolism, and an acceleration of the velocity of chemical processes with stimulation of glandular activity (8, 49, 90). The relief of vascular spasm (5, 18, 38), the counteraction of acidosis by the hyperventilation produced (91) and stimulation of the reticulo-endothelial system (27, 92) are other mechanisms that have received support.

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