VARIATION IN AGGLUTININ FORMATION IN MENTAL HOSPITAL PATIENTS AND ITS PROBABLE RELATION TO FOCAL SEPSIS.*

By F. A. PICKWORTH, B.Sc., M.B.,

Director for Joint Board of Research for Mental Diseases, City and University of Birmingham.

IT is well known that injection of protein substance into the blood causes the appearance in the blood of antibodies to the protein. Injection of bacteria is followed by the appearance of several kinds of antibodies, and the substances which produce "clumping" constitute one, or rather two, of these antibodies. The appearance of agglutinins in the blood following vaccination or infection has been shown to occur regularly in such a large number of individuals, and in animals, that there can be no doubt that this production of antibodies is a natural phenomenon connected with successful resistance to the deleterious effects of the organisms. Non-production or abnormalities in the production of agglutinins following injection of bacteria represents a pathological process probably of the nature of sepsis.

The following figures illustrate the reaction of a series of mental hospital patients to intravenous injections of T.A.B. vaccine.

Fig. 1 shows the average of 50 cases, and may be taken as a control of the remaining figures.

Fig. 2 shows an approximately normal curve, and indicates by lines below the scale that other Salmonella and dysentery agglutinins are not produced. One would expect similar curves from every normal individual.

Fig. 3 shows the reaction of another patient to the same vaccine given from the same bottles and at the same time. I have asked many eminent pathologists and bacteriologists why in this case there is no measurable reaction to the *Para. A* and *Para. B* antigens which have been injected, but it appears that the cause is not yet known.

Fig. 4 is of interest in that it shows that after an interval of four months there was again no reaction to *Para. B*, even although there was no doubt that the antigen of *Para. B* was injected into

* A paper read at the Annual Meeting held at Wakefield, July 13, 1928.

the system. The same slide also shows the appearance of agglutinins to Gaertner (G.) and Aertrycke (M.), whose antigens were certainly *not* injected with the vaccine.

One individual, whose reactions to typhoid are distinctly abnormal, shows an exactly similar type of Gaertner (G.) and Aertrycke (M.) agglutinin formation at an interval of five months (Fig. 5).

Fig. 6 shows the appearance of agglutinins to Aertrycke (M.) and dysentery Y, but what is of greater importance is the rapid disappearance of all the agglutinins within a few weeks. It may be remarked that in a healthy soldier agglutinins after vaccination often persist much longer than two years.

Fig. 7 is shown as an interesting result in which the response to vaccination with T.A.B. gives an enormous amount of agglutinins to Aertrycke (Mutton and Newport), and practically no reaction to typhoid.

It is impossible to discuss fully the many problems which arise from these abnormal reactions. They probably have a similar cause to that which is put forward in connection with one of them, namely the rapid disappearance of agglutinins.

It has been shown that injection of bacterial antigen may cause a production of agglutinins for other similar organisms, although the quantity is very small in comparison with that specific for the bacterium injected. It is also known that the injection of a sharply specific antigen such as typhoid or paratyphoid A may, in a person who previously has a titre to another organism, cause the production of agglutinins in a manner quite independent of, and without affecting this titre. Further—and this may seem somewhat paradoxical—the injection of an antigen, especially if less specific, *e.g.*, *Para. B*, may cause the appearance of agglutinins to a heterogeneous organism as has been shown in Figs. 4, 5, 6 and 7. It is reasonable to expect that an individual who has had the mechanism to produce certain agglutinins trained in consequence of infection would, on any subsequent stimulus of infection of similar although not identical nature, continue to produce agglutinins to the organism of the first infection. However, this argument is probably fallacious, since it might be that there remains somewhere in the system organisms of the first infection which might possibly gain entrance into the blood-stream when the resistance is temporarily depressed by some other infection, or by injection of a not too dissimilar antigen. Wright and Lamb found that infecting micro-organisms could grow in such regions as a blocked capillary or lymph-vessel in which antibacterial substances were absent or diminished.

Agglutinins may disappear from the blood in febrile conditions caused by infection or chemical agents, although the irregularity of

this phenomenon has given rise to some controversy. The records of the medical history of the Great War show that after the height of an enteric infection has been passed, the agglutinins to a heterologous organism often fall to one-fifth of the original titre. Besredka found that feeding animals with organisms a few months after a previous vaccination with the same organism caused the titre to fall from a high figure to an extremely low level. It is obvious that previously high agglutinins may be reduced by the cessation of production of the particular agglutinin, coincident with the process of alteration or destruction of the existing serum-globulin, such as occurs in fever, or in an urgent demand for the neutralization of large quantities of other antigenic substances which have found their way into the system. One of our own cases of suspected typhoid gave only a trace of agglutinin (below 7 Oxford units) on two occasions, but had a Gram-positive bacillus in the blood. *Post-mortem*, *B. typhosus*, agglutinating in high dilutions, was recovered from the liver, spleen, kidney and a nodule in the aorta.

The main part of this paper, however, is a consideration of how the system may be invaded by organisms with the production of antibodies for their destruction and removal from the system. It is known that the upper part of the small intestine is sterile, and that the colon type of bacilli are abnormal when they occur above the lower part of the jejunum (1).

Knott, Bogendorfer, Gorke and others find that in cases of achlorhydria the bacterial contents of the duodenum and ileum tend to be fæcal in type. "The organisms normally present in the jejunum evidently migrate to higher levels—a fact clearly illustrated by the results of routine examination of specimens from over 200 cases obtained *viâ* the duodenal tube" (1). Arnold and Brody note that in conditions in which the reaction of the duodenum is neutral or alkaline for any length of time, the bacterial flora changes to that found in the ileum or cæcum. Abnormal organisms in the upper duodenum undoubtedly occur in such conditions as pernicious anæmia (2).

It is a common mistake in medicine to lay too much stress on the exact type and variety of the infecting organism. *Paratyphosus A* and *Para. B* are quite dissimilar organisms, but produce similar clinical disease. Robinson tested 150 strains of *B. typhosus* serologically and found that none reacted alike. Durham considered that many varieties of the typhoid organism might be present in an attack of the disease, and that the system, on recovering from one, might be attacked by another. Mayer and Neilson state that a person immunized against typhoid may become infected, and when this occurs the bacilli may be so altered that they are not recognized;

however, such bacilli on gaining access to a non-immunized person may regain the typical characteristics of *B. typhosus*. In typhoid fever organisms are present continuously in the upper part of the duodenum, where they may, and often do, persist long into convalescence, and it is surmised that organisms of the typhoid and food-poisoning groups all possess this property of living high up in the small intestine.

It has been shown by the analogy of feeding animals with peptonate of iron (3) that the leucocytes of the intestines take up bacteria in the same manner as they take up food, and transport them to the liver and spleen, where, according to Adami (3), "the bacteria so transported multiply until the tissues react, causing their lysis, and the liberated toxins then destroy the neighbouring tissue . . ." "They represent not simultaneous infection but the summation of a succession of minute assaults on the tissues, sometimes occurring in a few days or weeks, but often extending over years." Desgorges describes a similar process, by which the bacteria find their way into the thoracic duct, and thence into the blood. Tissue invasion and bacteriæmia from high intestinal sepsis therefore accounts for an urgent demand for agglutinin formation through the presence of new deleterious bacterial protein.

An important connection between intestinal and focal sepsis is apparent from the above, when we consider the probable fate of some of the leucocytes whose function it is to procure food in the manner described. In high intestinal sepsis enormous numbers must be poisoned as they reach the intestine, following ingestion of organisms, and probably never return to the system; or if they do they may die on reaching the liver. This may account for the leucopenia in typhoid fever and pernicious anæmia, and for that occasionally found in cases of mental disorder associated with conditions of focal sepsis that would tend to cause leucocytosis, and it may possibly account for the variations in the leucocyte count in cases of mental disorder. There is an undoubted relation between the leucocytes and the formation of agglutinins as shown by Stenstrom, Moreschi and Howell. We have examined specimens of fæces from dysentery patients which consisted almost entirely of leucocytes. We have, therefore, a possible explanation of two important causes of focal sepsis, *i.e.*, a bacteriæmia and a depletion of leucocytes.

Garrod pointed out that "bacterial infections do not necessarily cause disease; only when the body begins to defend itself against attack does trouble arise." Bacteriæmia does not necessarily involve a fatal septicæmia when the bactericidal condition of the blood is high for the particular organisms which are able to enter

the blood-stream. Such organisms as are not immediately killed; however, can exist only in a state of extreme inhibition such as occurs when grown in immune sera; but just as in the experiments of Parish and Okell it was found that a non-fatal injection of streptococci *plus* anti-serum produced late secondary effects such as purulent arthritis, so intestinal organisms in similar circumstances may give rise to focal sepsis, as in typhoid osteitis and probably in apical infection of teeth. The organisms are not necessarily all pyogenic, or if pyogenic, do not always produce pus in a system depleted of leucocytes in the manner described above. Another important effect of high intestinal infection is that the individual suffers from starvation, with its deleterious consequences, and is supplied with bacterial toxin instead. Special food-stuffs, *e.g.*, vitamins, may become useless by non-absorption, destruction or excessive utilization, giving a condition worse than simple starvation (4).

Fig. 8 shows dilatation of the stomach in vitamin deficiency—itself a cause of high intestinal infection. Webster found that vitamin-rich food protected mice against typhoid: 15% only were fatal as against 100% controls. McCarrison showed that deficiency of vitamin B in wild monkeys rendered the intestinal tract susceptible to invasion by bacteria. His description of the *post-mortem* findings in such conditions might apply to almost any case of mental disease. It has been our experience to find almost constantly dilatation, ballooning, discoloration and congestion of some parts (not usually the whole) of the small intestine, with thinning of muscular coats and atrophy of the mucosa and the occurrence of enlarged lymphatic glands, which leave no doubt that chronic bacterial invasion from the upper part of the small intestine is common, if not universal, in the acute phases of mental disorder. Clinically it is known that undigested food may remain in the stomach of insane persons for eighteen hours or more. The frequent occurrence of delusions of poisoning further substantiates the theory of gastro-intestinal sepsis; indeed the symptoms of delusions of poisoning and of refusal of food should be taken as evidence of disordered conditions of the intestinal tract, the subjective disturbances of which are dimly recognized by the patient.

Local damage to the intestinal epithelium allows the entrance of other undesirable organisms or their toxins, especially *B. Welchii* and the streptococci. The character of the normal intestinal epithelium is such that there is a selective absorption of material useful for food. When this epithelium becomes damaged then this property must necessarily be disturbed, allowing the absorption of deleterious products of bacterial action, which is without doubt

detrimental to the general health. If the products formed are toxic to nervous structures, this will give rise to intellectual and emotional deterioration or to specific nervous effects such as occur with botulinus toxin. Bacteria interfere with the normal digestive processes in yet another way by producing highly toxic products by decarboxylating certain protein constituents, giving amino-compounds which are amongst the most powerful pharmacological substances known. For example, tryptophane by decarboxylation gives the poisonous indolethylamine, whereas if it is previously deamidized its products are harmless. Similarly the useful and non-poisonous histidine on decarboxylation becomes iminoazoethylamine, actually found by Boyd in the intestinal mucosa of children dying from intestinal toxæmia. Chronic poisoning by these products further weakens the resistance of the tissues to the associated high intestinal sepsis. Bolton and Salmond describe anti-peristalsis in the duodenum as a normal physiological process, and regurgitation through the pylorus is not at all uncommon, as evidenced by the traces of bile and even of pancreatic secretion found in test-meals. In high intestinal sepsis the organism thus obtains access to the stomach, and if vomiting occurs, even the nasal sinuses may be reached.

That organisms of the paratyphoid (Salmonella) class occur in mental hospital patients has been repeatedly emphasized in the past, and this is all the more interesting in view of the findings of Price-Jones. When a colony of rats is infected with Gaertner bacilli, the survivors contain these bacilli in the spleen and liver. After five months some Gaertner bacilli may be still present; the rats appear healthy, but can initiate an epidemic of Gaertner if placed with normal rats. Stewart finds Gaertner agglutination in mental hospital patients, and many varieties of organisms of the Salmonella (food-poisoning) groups in the fæces.

Organism.	Total agglutinations.		One organism only agglutinated.		Mixed agglutinations.	
	Number.	%	Number.	%	Number.	%
B. typhosus	353	11·5	199	6·5	154	5·0
B. paratyphosus A	108	3·5	19	0·6	89	3·0
B. paratyphosus B	155	5·0	48	1·6	107	3·5
B. paratyphosus C	45	1·5	14	0·5	31	1·0
B enteritidis (Gaertner)	141	4·6	70	2·3	71	2·3
B. aertrycke (Mutton)	114	3·7	55	1·8	59	1·9

This table does not include known vaccinated cases.

FIG. 9.—Agglutination Results, 1925–1928. Total specimens examined, 3,074. Positive, 916 = 29·8%.

Fig. 9 shows our figures for 1925–8, and indicates that 30% of specimens of serum from mental hospital patients agglutinate pathogenic organisms of the typhoid-food-poisoning bacterial groups; of these *B. Gaertner* is very predominant.

A vicious circle is established when focal sepsis affects the upper respiratory tracts, as, for example, in sphenoidal sinusitis.

Fig. 10 shows an infected sphenoid which is obviously continually pouring out pus to be swallowed, thus producing local damage of the stomach and intestine. Further, by local spread of toxins from the sinus the pituitary-hypothalamic region of the brain is affected, one probable effect of which, as occurs with temperature, fatigue and

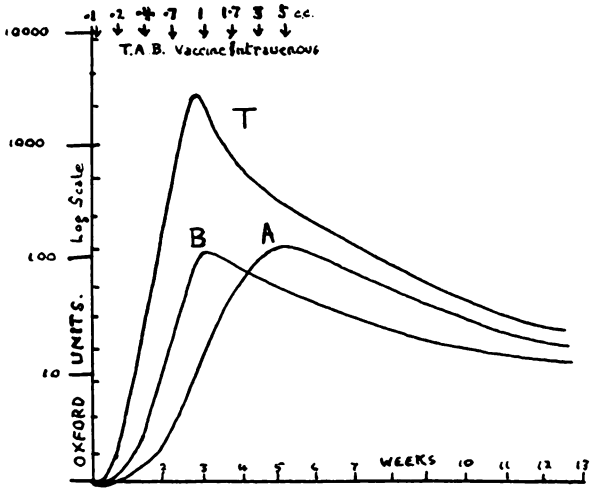


FIG. 1.

emotional disturbances, is a central inhibition of gastric secretion. Organisms of the intestinal type are not uncommon in the nasal sinuses, and the possible relation of these to intestinal infection is shown by analogy with the following case: "A well-built private, wounded in the tibia in the Great War, contracted typhoid in the base hospital in Mesopotamia in 1916. He recovered, but became a carrier of typhoid, in addition to which his wound did not heal. He was invalided home and deteriorated to a physical wreck until in 1919, when he was still a typhoid carrier; at an operation for cleaning the wound of the tibia the anæsthetist insisted on the removal of false teeth; the man protested, saying they had not been taken out for eight years. The anæsthetic had to be administered before the plate could be removed. The foul-smelling plate was

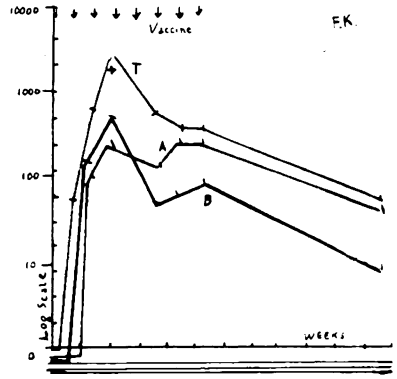


FIG. 2.

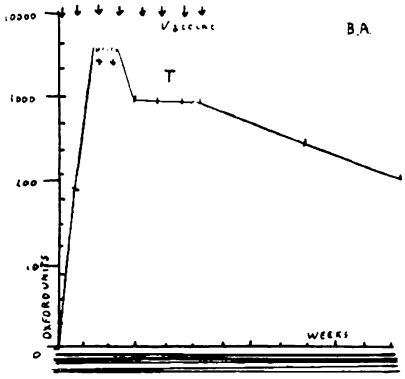


FIG. 3.

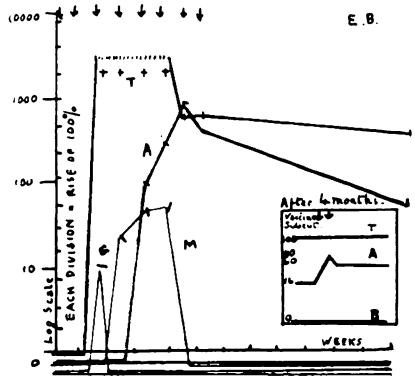


FIG. 4.

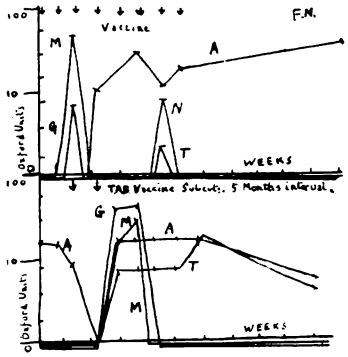


FIG. 5.

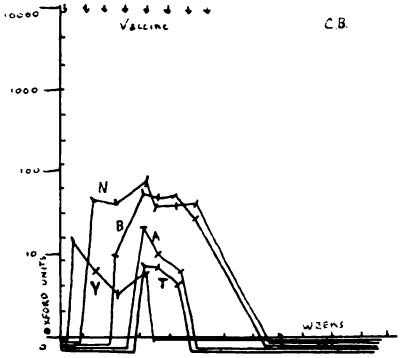


FIG. 6.

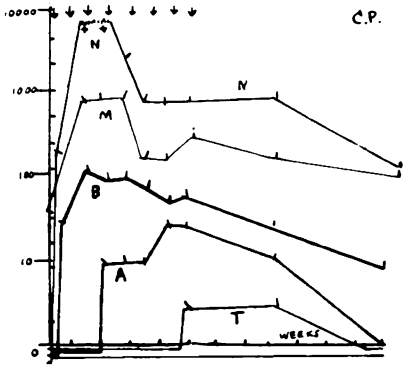
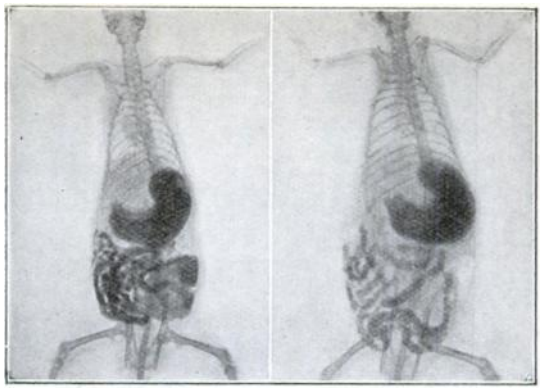
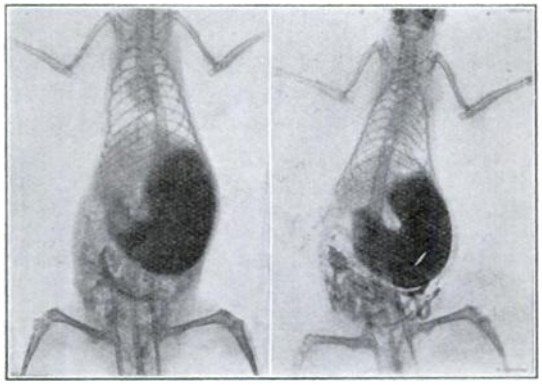


FIG. 7.

https://doi.org/10.1192/bjp.74.307.709 Published online by Cambridge University Press



Radiogram of control rats fed on normal diet.



Radiogram of rats fed on a diet deficient in vitamin B, showing ptosis and dilatation of the stomach.
Rowlands & Browning, 'Lancet,' 1918, i, 180.

FIG. 8.

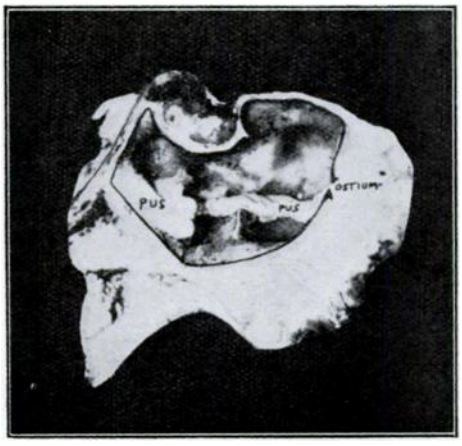


FIG. 10.

https://doi.org/10.1192/bjp.74.307.709 Published online by Cambridge University Press

FIG. 11.

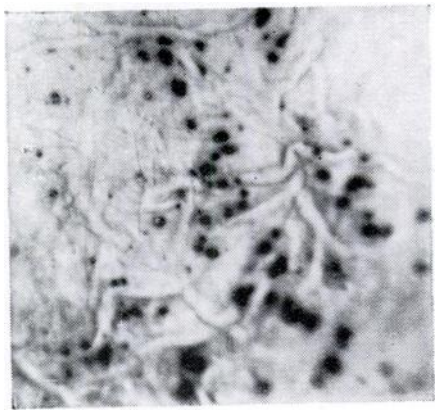


FIG. 12.

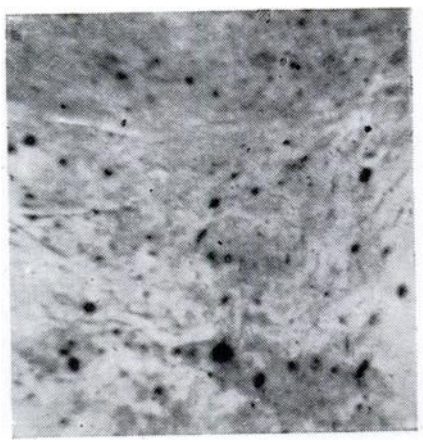


FIG. 13.

https://doi.org/10.1192/bjp.74.307.709 Published online by Cambridge University Press

sent in a sterile dish to the bacteriologist, who reported it to be 'loaded with typhoid.'"

Inflammation of the sphenoidal sinus has also been shown to be a probable primary cause of a diplococcal septicæmia which produced thrombosis of the small vessels of the stomach and the striking hæmorrhagic condition seen in Fig. 11. There were practically no organisms on the surface of the mucosa in this case so that there can be no doubt as to the cause of the condition being a thrombosis of the deeper vessels of the stomach by a hæmatogenous infection.

The two figures, 12 and 13, show these hæmorrhages in different stages of resolution, finally resulting in superficial erosions, pitting and atrophy of the mucosa. It is remarkable that gastric irritation was noted to be associated with mental disease by Broussais as early as 1822.

Local damage of tissue in a patient with bacteriæmia may result in focus of bacteria, which, even if dead, exert a deleterious local effect and prevent rapid and complete healing, as in the non-healing of the tibia of the typhoid case mentioned above. It is submitted, for example, that should a person develop acute sinusitis by infection with Pfeiffer's influenza bacillus at a period when there is a bacteriæmia from a high intestinal sepsis, then a chronic nasal sinusitis is much more likely to result than in a normal person similarly infected with influenza.

The inter-relation between focal sepsis and the variation in agglutinin-formation of the insane may therefore occur through the medium of a high intestinal sepsis caused or induced by infection with paratyphoid or food-poisoning organisms. Poisoning and loss of leucocytes in the intestinal tract, a bacteriæmia of intestinal organisms, most of which are rapidly killed, and re-infection from pyæmic focal sepsis originally caused or initiated by the bacteriæmia, are highly probable factors in this relation.

References.—(1) Knott, *Guy's Hospital Reports*, January, 1927.—(2) Van der Reis, *Klin. Woch.*, 1922, i, p. 950.—(3) Adami, quoted by Heyd and Killian, *The Liver in Chronic Abdominal Infections.*—(4) Forster, quoted by Cramer, *Lancet*, 1921, ii, p. 1202.

Bibliography.—Arnold and Brody, *Journ. Infect. Dis.*, 1926, xxxvii, p. 672.—Besredka, *Immunization Locale*, 1925.—Boyd, *Arch. Int. Med.*, 1923, xxxi, p. 297.—Desgorges, *Riv. de Med.*, 1927, ii, p. 163.—Durham, *Report on Colitis*, 1901, King & Co.—Garrod, *Huxley Lecture*, Charing Cross Hospital, 1927.—Howell, *Arch. Int. Med.*, 1920, xxvi, p. 706.—Manwaring, *J. Immunol.*, 1923, viii, p. 83.—Mayer and Neilson, *Journ. Infect. Dis.*, 1920, xxvii, p. 46.—*Medical History of the Great War: Pathology*, p. 239.—McCarrison, *Proc. Roy. Soc. Med.*, 1925, p. 3.—Parish and Okell, *Lancet*, 1927, i, p. 71.—Price-Jones, *Journ. Path. and Bact.*, 1927, xxx, p. 1.—Robinson, *Journ. Bact.*, 1923, viii, p. 53.—Salmond, *Proc. Roy. Soc. Med.*, 1928, xxi, p. 1361.—Stewart, *Journ. Ment. Sci.*, 1925, p. 622.—Wright and Lamb, *Lancet*, 1899, ii, p. 1727.