EXPERIMENTAL STUDIES ON THE CONNECTION OF SCHIZOPHRENIA AND TUBERCULOSIS.*

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Kraepelin and Morel were the first to emphasize the fact that tuberculosis is more common in schizophrenics than in other psychotics. Later on, Ganter, Zalla and Bonasera confirmed this statement with the support of a wide statistical inquiry. Thus Ganter found the mortality from tuberculosis in schizophrenics to be from 46 to 67%, whilst the general mortality-rate in tuberculosis in the Prussian asylums was only 16·6%; Bonasera found the tubercular mortality-rate to be 61·7%, and Zalla 67·5% in their autopsies on schizophrenics.

A recent paper by Bogen, Bogen-Tietz and Grace suggests that such statistics must be considered with much caution, the true facts being sometimes obscured by different sources of error, such as failure to consider the influence of the duration of the disease and the age of the patients. These authors demonstrated that the incidence of tuberculosis increases with the length of stay in the institution in all types of psychosis. This increase, according to the authors, is due to hospital infection. In addition, the incidence of tuberculosis was found to be highest in patients below the age of 40. Thus, for instance, a comparison of the tuberculosis morbidity of paralytics and senile dements admitted to the mental hospitals at a comparatively advanced age when tuberculosis infections are less frequent, with the morbidity of schizophrenics, in whom the disease appears at a much earlier age, may lead to gross statistical errors. Even if all possible sources of error were excluded, the statistical comparison would only demonstrate a coincidence of two pathological processes. No conclusion could be arrived at as to a causative connection between both diseases, although such an assumption has been made by some authors who have classed dementia præcox as a "metatuberculous" disease. The question whether there exists any connection of this kind can only be decided by experimental research.

The question has been reopened of late by the work of Loewenstein, who claims to have found, by the method of culture, tubercle bacilli in the blood in 38% of cases of schizophrenia. Later on, he also claimed to have demonstrated these bacilli in the cerebro-spinal fluid. His findings have been examined by several workers, but have been confirmed only by Puca.

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On the other hand, blood-culture experiments have been reported to be negative by Meyer and Schaede in 50 cases, by Kottman in 20, by Beck in 125, by Rodiet, Nevot and Maillefer in 18, by Saënz, Pascal, Costil and Chapoulard in 41, and by Anadiades, Papanargyrou and Scouras in 14 cases of schizophrenia. The cerebro-spinal fluid cultures of Fernandez in 31 cases, of Beck in 41 cases and of Anadiades, Papanargyrou and Scouras in 7 cases also yielded only negative results.

Shortly after the first publications of Loewenstein's work, Toulouse, Schiff, Valtis and van Deinse, and later Claude, Valtis, Coste and van Deinse, claimed to have demonstrated the tubercle bacillus in the blood and cerebro-spinal fluid of schizophrenics by inoculation of these fluids into guinea-pigs subsequently treated by injections of an acetone extract of tubercle bacilli. According to the French authors, this extract, if injected over a longer period, favours the development of tuberculous infections, especially of infections due to the "tubercle ultravirus", which they presume to be the ætiological factor of schizophrenia. With this method they claim to have demonstrated the tubercular virus in 55·6% of the cases. Sometimes tubercle bacilli could be demonstrated in the primarily injected animals, sometimes only after several further animal passages.

Puca, and also d'Hollander and Rouvroy, claim to have demonstrated tubercle bacilli in schizophrenics by means of animal experiment. But Puca restricted himself only to the microscopic demonstration of acid-fast bacilli in the lymphatic glands, whilst the statements of d'Hollander and Rouvroy, as already pointed out by Claude and his collaborators, give rise to doubts as to the true tubercular nature of the changes referred to.

During the time that these experiments were carried out, reports have been published by Saënz, Pascal, Costil and Chapoulard, as also by Fernandez, emphasizing the wholly negative results of their animal inoculations with 41 bloods and 20 cerebro-spinal fluids from schizophrenics. As far as can be gathered from their reports, the authors did not exactly follow the technique of Valtis and van Deinse, in that they omitted the treatment of the animals with the acetone extract of tubercle bacilli. This treatment is claimed by Valtis and van Deinse to be indispensable, untreated controls injected with blood or cerebro-spinal fluid of schizophrenics remaining quite negative in their experiments. Moreover, Saënz and his collaborators do not seem to have made any reinoculations from their injected animals.

In the meantime a paper was published by Claude and Coste in which these authors no longer support their previous experimental results obtained in collaboration with Valtis and van Deinse. They report that new experiments in their own laboratory have remained quite negative, and that control examinations carried out in the laboratory of Valtis and van Deinse have yielded positive results also in cases of general paralysis and other non-schizophrenic psychoses.

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Besides the direct demonstration of tubercle bacilli which, of course, would be the clearest proof of the tuberculous origin of schizophrenia, attempts have also been made to elucidate the problem by indirect methods, such as the study of tuberculous antibodies in schizophrenia. Thus the presence of complement-fixing tuberculous antibodies in the blood and cerebro-spinal fluid, of tuberculous antigen in the cerebro-spinal fluid and of skin-reagins with tuberculin have been sought for. Abély claims to have found complement-fixing antibodies in the serum of 70% (!), Vie in 26%, Hamel in 37%, Kindermann and Hoffmann in 13%, Puca in 57 (!) out of 87 cases, Baldi in 36·7%, Beck in 21·5%, and Dide, de Boissezon and Aujaleu in 7 out of 67 cases of schizophrenia. The small absolute percentage of positive reactions has led Beck, Baldi, Kindermann and Hoffmann, Dide, de Boissezon and Aujaleu to the conclusion that the complement-fixation test gives no support to the theory of a tuberculous origin of schizophrenia.

The tubercular complement-fixation in the cerebro-spinal fluid was found by Hamel to be positive in 6 out of 8 cases of schizophrenia, whilst Beck, examining 12 cases of schizophrenia, never found a positive reaction. Even in tuberculous meningitis this reaction was found by him to be positive in only 4 out of 10 cases. He also was unable to demonstrate any tubercular antigen in the cerebro-spinal fluid either of schizophrenics or of patients suffering from tuberculous meningitis.

In the examination of tuberculin reactions no difference was found as to the frequency of positive reactions between schizophrenics and other psychotics (Baldi, Beck). Likewise Bogen, Bogen-Tietz and Grace found the frequency of this reaction to be dependent only on the duration of the stay in hospital of the patients irrespective of the nature of their psychosis. On the other hand, Beck claims to have found the reaction to be often more intense in schizophrenics than in other psychotics. This has also been observed by Baruk.

The last-mentioned author also claims to have demonstrated a tuberculin-like substance in the cerebro-spinal fluid of a schizophrenic. The inoculation of this fluid into a tuberculous guinea-pig was followed by a skin reaction which Baruk identifies with the typical tuberculin reaction. Later on, the animal showed signs of stupor and catatonia, which the author considers to be due to a tuberculotoxic effect on the brain. Fernandez, repeating these experiments with cerebro-spinal fluids and brain extracts of schizophrenics, was unable to confirm them.

From the above review of the literature it follows that the question of the tuberculous genesis of schizophrenia has neither been confirmed nor disproved. Although Loewenstein's cultural findings are weakened by the great number of negative results in other laboratories, they are on the other hand indirectly supported by the positive animal experiments of Valtis and his collaborators. These, up to the present, have not been exactly repeated.

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The Present Experiments.

In view of the importance of the problem further experiments seemed to be desirable, and these have been carried out at the suggestion of Dr. F. L. Golla. The investigations on schizophrenics* included: serological examinations, (*a*) for a tuberculin-like antigen in the cerebro-spinal fluid, and (*b*) for tuberculous complement-fixing antibodies in the serum; examinations for the presence of tubercle bacilli in the blood and cerebro-spinal fluid, (*a*) by two different cultural methods, and (*b*) by means of animal experiment. As a control of the efficacy of the two last-mentioned methods, a number of tuberculous human and animal blood samples were examined simultaneously.

I. *Examination of the Cerebro-spinal Fluid for the Presence of Tuberculin-like Antigen.*

We used in this investigation white (albino) guinea-pigs infected six weeks previously by the injection of 0·1 mgrm. of a culture of tubercle bacilli or of tuberculous milk. 0·1 to 0·2 c.c. of cerebro-spinal fluid was injected intradermally in the depilated flanks of the guinea-pig. At the same time a control injection of 0·1 c.c. tuberculin (diluted 1 : 10) was made. Each of the 24 cerebro-spinal fluids were tested on at least two animals.

The injection of the unaltered cerebro-spinal fluid from cases of either schizophrenia or tuberculous meningitis, did not give any skin reaction, and in consequence the experiments were continued with concentrated fluids. These were obtained by drying the original cerebro-spinal fluid *in vacuo* over calcium chloride at room temperature, and subsequently dissolving the dried residue in distilled water from a fifth to a tenth of the original volume. But even with this method a true tuberculin reaction was never detectable either from cases of schizophrenia or—contrary to Nasso's statement—from cases of tuberculous meningitis. There were also no signs of catatonia or stupor—as described by Baruk—observed in the animals injected with the cerebro-spinal fluid of schizophrenics.

II. *The Complement-fixation Tests in the Blood.*

In these experiments each serum was tested both with the antigen of Witebsky, Klingenstein and Kuhn† (W.K.K. antigen) (1931), and with a methyl antigen prepared by the writer according to the technique of Boquet and Nègre (1927). At first the sera were also tested with the precipitation reaction of Lehmann Facius (1926), but, later, this reaction was abandoned because of its non-specificity. In order to exclude in the complement-fixation

* It should be noted that recent cases were chosen, as in these the disease could be still developing.

† I am indebted to Prof. H. Schmidt, Behringwerke, Marburg, Lahn, who has put this antigen at my disposal.—A. B.

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test any non-specific reaction due to a positive Wassermann, each serum was also tested with a syphilitic antigen.

197 sera have been examined, 124 of them derived from dementia præcox cases, the remaining 73 from other mental diseases (epilepsy, manic-depressive states, secondary dementia, delusional states, etc.). These results are set out in the following table :

Dementia præcox.					Other psychoses.				
Number of cases tested.	Sex.	Positive with WKK antigen.	Positive with methyl antigen.	Percentage of positive cases.	Number of cases tested.	Sex.	Positive with WKK antigen.	Positive with methyl antigen.	Percentage of positive cases.
95	Male	4	5	5·3	45	Male	3 (1)	5	11·1
29	Female	5 (1)	5 (2)	17·2	28	Female	2	4 (1)	14·3
124	..	9	10	8·1	73	..	5	9	12·3

(The figures in brackets indicate doubtful results.)

The principal fact arising from this table is that there is no essential difference in the frequency of positive reactions in schizophrenics compared with other psychotics.

Considering the total numbers, and especially those in the male group, there is even a slight difference in favour of the control group. The percentage of positive reactions in male schizophrenics approaches the percentage found in a normal population, which is according to Hoering (1932) 4%, and according to Beck (1933) 3·5% (both authors working with the W.K.K. antigen).

Further experiments will have to be undertaken to explain why the complement-fixation reaction was found more frequently positive in females. The male patients were in a different hospital from the females, and it will first be necessary to determine if these results are due to a difference of local conditions before assuming that female patients are more liable to tuberculosis.

Summarizing, therefore, the results of the tubercle complement-fixation test, it may be stated that the relatively low percentage of positive reactions, together with the lack of difference in their frequency in schizophrenics and other psychotics, would make a causative connection between tuberculosis and schizophrenia improbable.

III. *Cultural Examination of the Blood.*

This was carried out by the following two methods :

(1) *Method of Loewenstein* (1932) (solid medium).—6–8 c.c. of sterile citrated blood were obtained. After centrifuging, the plasma was discarded, and 5–7 times the amount of distilled water added to hæmolyse the corpuscles. If the hæmolysis was not complete this process was repeated. The hæmolysed blood was centrifuged for half-an-hour. The deposit was mixed with an equal volume of 10% sulphuric acid for 5 minutes, then washed twice with distilled water and inoculated

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on three Loewenstein-Jensen slopes.* We used the screw-capped bottles introduced by McCartney (1933, 1934) for culture media. The screw cap renders unnecessary a seal of paraffin wax or other material. The media bottles were kept in the incubator for 3 months.

(2) *Method of Ninni-Bretey* (1933) (fluid medium).—8 c.c. of sterile citrated blood were added to 20 c.c. of Sauton's medium in 10-oz. screw-capped bottles and incubated for 28 days. For the first 2 weeks the media bottles were slightly shaken every second day. After 4 weeks they were examined microscopically, and a subculture was made on Loewenstein-Jensen medium.

Blood samples from 31 schizophrenics have been examined. Twenty-six of them by both methods, 5 by one only.

In none of the cases of schizophrenia examined by the method of Loewenstein was it possible to demonstrate tubercle bacilli, either macroscopically or microscopically. No result was obtained with the blood-cultures in the Sauton medium and their further subcultures on the Loewenstein medium. On the other hand, control examinations of heart-blood samples of known tuberculous infections (34 guinea-pigs, 1 rabbit, 1 cock, infected with tuberculosis) gave a positive result in 30·5%, thus proving the efficacy of the method used.

Thus it may be stated that the blood-culture from schizophrenics carried out with two different methods gave no evidence for tuberculous bacillæmia in this disease.

IV. *Examination of the Blood and the Cerebro-spinal Fluid by Animal Inoculation.*

In these experiments we followed the technique of Claude, Valtis, Coste and van Deinse (1933). 8–10 c.c. of sterile citrated blood, or of cerebro-spinal fluid were injected intramuscularly into guinea-pigs of average weight. In some of the experiments this amount of material was distributed among several (up to 5) guinea-pigs, so that each animal received 2–4 c.c.. By so doing it was intended to avoid a break in an experiment by the premature death of the animal, and to diminish as much as possible any errors due to differences in the resistance of the animals. The guinea-pigs were subsequently injected twice a week throughout the whole duration of the experiment with 1 c.c. of an acetone extract† of tubercle bacilli.

The animals were kept under observation for 3–4 months, some of them up to 7 months. In some guinea-pigs this period was shortened by premature death. The lymphatic glands and spleen of the spontaneously dead and of the killed animals were reinoculated after autopsy into other animals, since according to

* The preparation of this medium is given by Mackie and McCartney (1934), and its value in the cultivation of tubercle bacilli is described by Holmes (1934).

† The technique seen by one of the authors in the Pasteur Institute, is as follows: 6 weeks old cultures of tubercle bacilli (strain T.B. bovine Vallée, and T.B. human Test) grown on glycerin broth in screw-capped bottles were killed by heating at 120° C. for half-an-hour, then thoroughly washed, dried and pulverized. They were then extracted for 2 days with pure water-free acetone (100 c.c. per gramme of bacilli), the suspension being shaken repeatedly during this time. The extract was filtered from the bacilli, and diluted with an equal amount of distilled water. The acetone was allowed to distil over at 45° C. ***in vacuo***, the acetone soluble lipoids remaining in a watery emulsion. This was sterilized by heating at 56° C. for 1 hour. For the first series of our experiments an acetone extract kindly supplied by Drs. Valtis and van Deinse was used.

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Valtis and van Deinse the tubercular ultravirus is often only demonstrable after many passages. At the autopsy special attention was paid to the lymphatic system. The inguinal, lumbar, mesenteric, tracheal and cervical glands were examined macroscopically, and several of them, as well as the spleen, and sometimes also the liver and the lungs, were examined microscopically for the presence of acid-fast bacilli. In addition in each case a culture on Loewenstein medium was made from the lymphatic glands and the spleen (using the modification by Saënz and Costil (1933) of Loewenstein's technique). Animals showing any changes suggestive of tuberculosis during life were tested intradermally with tuberculin (diluted 1 : 10). In order to ascertain whether tuberculous infections may be due either directly or indirectly to the acetone extract, a series of control animals was treated with the acetone extract alone.

Following the method above described, 29 samples of blood, 27 of cerebro-spinal fluid and 2 brains* of schizophrenics were examined.

In these experiments 205 guinea-pigs were used for primary injections, and 106 guinea-pigs for passage inoculations. In spite of this large expenditure of animals, the length of observation and the number of passages, carried out sometimes up to the fourth or fifth generation, none of the animals injected with blood or cerebro-spinal fluid from schizophrenics showed any signs of tuberculosis either in the post-mortem examinations or in the microscopical and cultural examinations. In one case only, microscopical examination of a fibrous cervical gland revealed acid-fast bacilli, but the other anatomical findings, the culture, as well as further passage inoculations of this gland, remained negative. It is probable that the bacilli found microscopically belonged to the group of acid-fast saprophytes repeatedly described, in the organs of guinea-pigs, and more recently by Kimura (1934) and Botzaris (1934). It is also possible that they were dead bacilli derived from the acetone extract.

The tuberculin reaction, carried out in some cases in which the glands by palpation were found to be suspicious, was always negative.

In some cases recent infections with the *Bacillus pseudo-tuberculosis rodentium* showed the same pathological changes described by Valtis and van Deinse as characteristic of infections with the tubercular "ultravirus". In these cases there was a swelling of the lymphatic glands and of the spleen without formation of nodules. The nature of these changes was determined by the microscopical demonstration of the causative bacilli or by their culture from the heart blood, and also by the negative result of the Loewenstein culture and of further animal inoculations. This infection, if of longer duration, could also produce nodules in the spleen and liver, but these are readily distinguishable from true tubercles.

Sometimes deep-seated muscle abscesses due to the repeated injections of the acetone extract were accompanied by a swelling of the regional glands. The discovery of the abscess and the cultural examination then revealed the

* In these cases ground-up material from the choroid plexus, and in one also ground-up parts of the basal ganglia, the cortex and white matter were inoculated. This material was controlled by cultures.

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nature of these lesions. Signs of cachexia as described by Valtis and van Deinse were not observed, except in those animals which had died from a spontaneous infection.

In contrast to the wholly negative results in schizophrenics, 2 out of 12 blood samples of a known tuberculous origin (10 human samples from pulmonary tuberculosis, and 2 samples from tuberculous guinea-pigs) gave positive results.

Thus it may be stated that guinea-pigs treated with acetone extract of tubercle bacilli, even through several animal passages, never gave evidence of the presence of tubercle bacilli in schizophrenics. On the other hand, with the same method tubercle bacilli have been demonstrated in cases of definite tuberculous infection.

Discussion of the Results.

The negative results of our blood-culture experiments are in accordance with all authors except those who collaborated with Loewenstein. Moreover, Loewenstein's assertions seem to be weakened by the fact that his other statements on tuberculosis and other diseases connected by him with tuberculosis have not been wholly confirmed by the majority of other workers (*vide* Wilson, Saënz, Kolle and Küster). It would exceed the scope of this paper to deal with the different interpretations of Loewenstein's work; we may refer to Wilson's recent monograph on tuberculous bacillæmia.

The validity of the statements of Valtis and van Deinse is considerably affected by the recent communication of Claude and Coste.

The demonstration of tubercle bacilli in cases of general paralysis and other psychoses would either presuppose the existence of tuberculous processes in all these diseases, or would suggest that spontaneous infections occurred in the experiments of Valtis and van Deinse. As there is no evidence which would help to support the first hypothesis, the results can only be explained by the second. This suspicion is supported by the fact that most of the strains isolated by Valtis and his collaborators resembled the avian type of the tubercle bacillus, except that they caused acidity in the Sauton medium. Owing to its higher resistance to external influences, this type is specially capable of producing spontaneous infections. Furthermore, it is possible that animals treated for a long time with acetone extract from tubercle bacilli become highly sensitive to a spontaneous tuberculous infection.

Besides the failure of the animal and culture experiments, there also was no evidence in our serological tests of the often alleged higher incidence of tuberculosis in schizophrenia. The contrary statements from other countries—even if the criticisms just given are not applicable—may still be reconcilable with our results. It is conceivable that a possible increased

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susceptibility to tuberculosis becomes evident only in unfavourable surroundings. The difference between our results and the conclusions of other authors might then be due to the different environmental conditions of the patients. But even if this is admitted, the connection of schizophrenia and tuberculosis would only consist in an equal frequency of both diseases in the same group of men. It might be possible that this fact is due to a parallel affinity of both diseases for the leptosome constitutional type (Kretschmer), or to a correlation between the hereditary tendencies of both diseases (Luxemburger). It may be stated that there is not the slightest proof of a causative connection between tuberculosis and schizophrenia afforded by our experiments.

Conclusions.

(1) The examination of the cerebro-spinal fluid of schizophrenics for the presence of a tuberculin-like antigen was negative.

(2) The complement-fixation test with blood-serum was positive in 8·1% of schizophrenics and in 12·3% of other psychotics.

(3) Blood culture for tubercle bacilli using the methods of Loewenstein and of Ninni and Bretey was carried out with 31 schizophrenics. In all cases the result was negative. The efficacy of the method used was proved by the positive results obtained with it in 30·5% of cases of known tuberculous infection in animals.

(4) The inoculation of 29 blood, 27 cerebro-spinal fluid and 2 brain samples from schizophrenics into guinea-pigs, which were subsequently treated with an acetone extract of tubercle bacilli, gave entirely negative results.

(5) These results indicate that there is no ætiological connection between schizophrenia and tuberculosis.

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