A daily estimation of the blood urea did not show any elevation during the experimental period. The reticulocyte count remained between 10 and 16 per 1,000 throughout the ten days following the first infusion. On the last day the haemoglobin was 44 per cent., the red cells numbered 1,450,000, and the white cells 2,800. There was no subjective amelioration, such as can often be observed under liver therapy before any change occurs in the blood picture.

Interpretation

According to Minot and Murphy (1927), if ten days elapse without the appearance of a reticulocyte reaction it can be concluded that the substance given is inactive.

There was no question of a state of aplastic anaemia, since the subsequent injection of liver extract provoked a clear reticulocytosis, rising from 31 per 1,000 on the fourth day to 180 per 1,000 on the seventh, with steady improvement of the anaemia until at the end of two months the patient left the clinic with 87 per cent. haemoglobin, 4,000,000 red cells, and a practically normal blood picture.

The doses of urine given in this case were not less than those employed by Decastello. In fact, the latter obtained reticulocyte reactions with daily infusions of 50 to 150 c.cm. (total dosage, 2,000 c.cm.) and clinical and haematological improvement with larger doses—300 to 500 c.cm. per day to totals ranging from 3,000 and 4,000 c.cm. up to 26,000 c.cm.

Obviously no definite conclusion can be drawn from this single case, and it is unfortunate that a similar trial could not be carried out on the other cases, either because their condition did not admit of delay in instituting treatment of known value or because they manifested the alimentary troubles characteristic of their malady.

Until more amply informed, we incline to the opinion of Wakerlin, who, after first demonstrating, as he believed, the presence of anti-pernicious principle in the urine, concluded in the light of further experiments that it was in fact absent.

Summary

1. Human urine, in health and in untreated pernicious anaemia, contains a substance capable of producing a reticulocyte reaction in the white rat.
2. Normal urine, in the case of pernicious anaemia described, showed no therapeutic activity.

BIBLIOGRAPHY

- Baráth, E., and Fülöp, J. (1935). *Klin. Wschr.*, **14**, 1077.
 Cohn, E. J., McMeekin, T. L., and Minot, G. R. (1930). *J. biol. Chem.*, **87**, xlix.
 Crosetti, L., Bajardi, G., and Margulius, M. (1937). *Klin. Wschr.*, **16**, 677.
 Dakin, H. D., Ungley, C. C., and West, R. (1936). *J. biol. Chem.*, **115**, 771.
 Decastello, A. (1935). *Med. Klinik*, **31**, 377.
 De Jong, J. J. (1938). *Nederl. Tijdschr. Geneesk.*, **82**, 863.
 Farrar, G. E., jun., and Sturgis, C. C. (1936). *Folia Haematol.*, **54**, 193.
 Feigin, M., and Plonskier, M. (1936). *Wien. klin. Wschr.*, **49**, 723.
 Fleischhacker, H., and Schlesinger, A. (1935). *Med. Klinik*, **31**, 182.
 Hitzengerber, K. (1934). *Klin. Wschr.*, **13**, 1345.
 Jéquier, E. (1936). *Rev. méd. Suisse rom.*, **56**, 880.
 Kamerling, A. W. C. G. (1935). *Wien. klin. Wschr.*, **48**, 1140.
 Leiner, G. (1935). *Ibid.*, **48**, 559.
 Levi, S. (1937). *Riv. Clin. pediat.*, **35**, 635.
 McCann, W. S. (1928). *Proc. Soc. exp. Biol.*, N.Y., **25**, 255.
 Mark, R. E., and Hauke, G. (1937). *Z. klin. Med.*, **132**, 705.
 Minot, G. R., and Murphy, W. P. (1927). *J. Amer. med. Ass.*, **89**, 759.
 Naegeli, O. (1936). *Helv. med. Acta*, **3**, 581.
 Singer, K. (1932). *Klin. Wschr.*, **11**, 1459.
 — (1934). *Ergebn. inn. Med.*, **47**, 421.
 — (1935). *Klin. Wschr.*, **14**, 200.
 — and Wechsler, L. (1936). *Ibid.*, **15**, 668.
 Tempka, T. (1936). *Polsk. Gaz. lek.*, **15**, 865.
 Wakerlin, G. E. (1936). *J. Pharmacol.*, **58**, 1.
 — (1937). *Ann. intern. Med.*, **11**, 31.
 Whipple, G. H., and Robschey-Robbins, F. S. (1925). *Amer. J. Physiol.*, **72**, 408.

THE EARLY DIAGNOSIS OF SCHIZOPHRENIA

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The recent application of new methods of treatment in schizophrenia (by hypoglycaemia and convulsions) has brought into the foreground the necessity for early diagnosis. Whatever their opinion of the absolute value of these new methods, all workers are agreed that the best results are obtained in early cases.

Many views are held as to the nature of schizophrenia. Some regard it as a distinct disease-entity, others as probably embracing a number of different morbid conditions, still others prefer to look on it as a preformed type of reaction shown at a certain level of cerebral disintegration. However that may be, up to now it can be diagnosed only by psychological means. This may change at any time. Biochemistry may provide us with a specific reaction for the whole or some of the cases we call schizophrenic; so may the study of the brain-waves, or any other method. There is perhaps some hope that even the modern therapeutic experiments may enable us to arrive at a physical method of diagnosis. But at present we still have to do without a "Wassermann" of schizophrenia.

Signs and Symptoms

In psychological medicine we cannot proceed, as in general medicine, by collecting signs and symptoms and fitting them into a sort of jig-saw puzzle. All the symptoms have to be related to the psychological background against which they appear. All the circumstances, even though they appear to be side issues, have to be taken into account, and the symptoms have to be evaluated in relation to the personality of the patient, his upbringing and education, and his present environment. Especial difficulty arises in cases with an insidious onset, slight but definite indications of which are often discovered in schizophrenics preceding the appearance of an acute illness.

The characteristic symptoms may be little marked or may be disguised by secondary features that are really the patient's reaction to morbid changes which may be as yet imperceptible. These insidious and slowly progressing cases are often mistaken for neuroses. It is important that they should not escape the attention of the physician, and that they should not be subjected to a prolonged and useless psychotherapy.

Three-quarters of the cases begin between the ages of 15 and 25. Slight depression, a tendency to oppose the older generation, and hypochondriacal concern about the bodily changes in later puberty are to some extent natural at the earlier age. But if these events are exaggerated and prolonged this may be a first premonitory sign. A well-educated, intellectually precocious youth changes from one profession to another, and seems quite unable to find his vocation in spite of all possible facilities and help provided by his relatives. A shy and seclusive girl exhibits an un-influencible stubbornness in her behaviour towards her friends, gradually losing all contact with her family, and becomes a member of a revolutionary sect or group in which also she is regarded as strange. Others go from doctor to doctor with vague complaints of fatigue and rapid exhaustion under comparatively slight stress, insomnia,

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general nervousness, etc. They look pale, have a greasy skin and sluggish vasomotor response; otherwise no bodily illness can be found. Or the patient may come to the physician complaining of sexual anomalies, in themselves perhaps usual enough in puberty, but described in a cool objective manner devoid of normal bashfulness or concern. Or prolonged shyness or sexual indifference may give place to an exorbitant self-indulgence, regardless of convention or social standards.

If the disease starts later, ideas of jealousy, well founded or not, may be a first premonitory sign, and are usually reported by the partner. Relatives complain to the doctor of a husband's ruthlessness to his wife and children and his lack of interest in his business. Neighbours find a previously gentle and sociable lady becoming suspicious, quarrelsome, and inaccessible to reasonable argument; she becomes slovenly and avoids any contact until the neglect of her children provokes the attention of the authorities.

This catalogue could easily be extended. But though one's suspicion may be aroused by the recital of such histories, the attention should be directed to more specific symptoms.

As elsewhere in medicine, the significant and diagnostically important symptoms in schizophrenia are not the most impressive ones. The order in which they are given here is that of their diagnostic importance.

I. Thought Disorder

Bleuler regarded the loosening and breakdown of normal processes of association as the fundamental disturbance in schizophrenia, and therefore invented that name. Thinking is not disturbed because it starts from wrong suppositions which lead it astray; this would be the description of a certain type of delusional ideas. In schizophrenic thought disorder the single contents may be correct in themselves, but they are put together in a muddled and scattered manner. "There is an abundance of what one might term 'the knight's move' in association" (Mapother). Therefore, the result of thinking if uttered or written down often sounds like a silly joke, although not meant as such.

To give a few examples. A patient wrote in a letter to the hall porter of a hospital from which the former was absent on week-end leave: "If I should return during my absence, keep me here until I come back." Fragment of an interview between patient and physician: (In what way do you feel ill?) "You know the story of Adam and Eve? How Eve was tempted with an apple?" (What about your illness?) "All the people in the ward eat apples." (That is not unusual!) "In the ward the door is open and the window closed." (Yes, I think that is so.) "Nobody will be able to get to the apple-tree. . . . We are all ruled by electricity, all except my dog," etc. A schizophrenic patient mentions Napoleon and goes on to say that he was banished to Ellis Island. "That's where they psycho-analyse people" (W. L. Woods).

If the disturbance is so striking it is easy to recognize. In the beginning of the illness it may be very slight and only demonstrable under certain circumstances—for example, if one asks the patient to repeat a story or to explain a proverb or the point in a fable. The disorder may even only be a subjective symptom to which the patients react with uncharacteristic complaints. They speak of inability to concentrate, or complain that their ideas are diffuse or narrowed. But often the disorder is not regarded as an incapacity by the patient; on the contrary, he brings forward his vague nonsense as something quite natural, and feels himself not understood by the

persons of his environment. Simple things are expressed in a queer stilted language, and are uttered in the tone of mystical revelations. A student turns from science to what he calls philosophy. Uneducated people think themselves able to reform human life and solve the deepest problems.

It is sometimes not easy to differentiate this behaviour from the transitional intellectual inconsistencies of the adolescent age. Thought disorder in confusional states (due to intoxications or other severe cerebral impairment) is often of very similar incoherent kind. But in confusional states there is always a dimming or clouding of consciousness, which is clear and unimpaired in schizophrenia. In cases in which the state of consciousness cannot be ascertained the history and the somatic findings mostly make clear the nature of the disorder.

II. Disturbances of Volition

Symptoms which can be classified under this heading are easily overlooked, and are often only disclosed by direct questioning of the patient. Then he will say that he does not feel master of his will, his thoughts, or his activities; he is influenced by other people who make him think or do things; his ideas, words, or movements are not his own, he feels hypnotized, drugged, etc. These disturbances of volition, if expressed straightforwardly, are pathognomonic of schizophrenia. But there is often only a slackening of will-power, which may not be realized by the patient himself. This can be one of the first signs: the patient becomes unable to make any decision in the various things of daily life, as well as in important questions like marriage or choice of a profession. Well-educated intelligent men become idlers or vagrants without any detectable cause. As in most other schizophrenic symptoms, the striking change in the patient's behaviour compared with his former habits is important here.

It is sometimes impossible to distinguish psychologically the loss of volition in commencing schizophrenia from weakening of spontaneity in a neurasthenic or in a patient with organic deterioration. Circumstances and concomitant symptoms usually make differentiation possible. Moreover, slackening of will is not often the only volitional disturbance in schizophrenics. It occurs together with spells of unexpected hyperactivity, of absurd impulses, and with specific schizophrenic anomalies known by the terms "negativism" (morbid contrariness without any motivation) and "ambivalence" (presence of opposite tendencies, between which no decision is made).

Signs of this kind, if present, also permit the distinction of volitional weakness in schizophrenia from retardation in depressive states. This differential diagnosis can be difficult, especially if the depressive affect is not very pronounced. The affective anomalies characteristic of schizophrenia will, however, be of help here.

III. Inadequacy and Incongruity of Affect

The normal emotions of affection and sympathy for the patient's nearest relations or friends cool off or take on a quality of shallowness during a commencing illness. More primitive emotional reactions—for example, of fear or rage—are preserved longer. Some patients notice and complain of this loss of all warmth of affection: a similar complaint is often made by depressives, who do, however, in the very moment of making the complaint, show a normal affective response. In many schizophrenics their cool and uncouth behaviour is only remarked by their relatives: the patients deny it, or find nothing strange in their tactless or flippant manners.

It is due to the loss of affective response of the early schizophrenic that the physician is often unable to establish a natural rapport with his patient, in spite of efforts to do so. This test, if cautiously applied, can serve as a valuable diagnostic aid—for example, in cases in which early schizophrenia is disguised in the form of a neurosis.

The difficulty is that many persons of a schizophrenic diathesis show an inadequate affective response all their lives. In such people the onset of the psychosis may be signalized by gross anomalies of emotional reaction—for example, fatuousness, an out-of-place hilarity, or (of great practical and medico-legal importance) an unfeeling cruelty. Murder and similar crimes are often attempted and committed by unrecognized schizophrenics. The percentage of schizophrenics in institutions for criminal lunatics is much higher than that in the average mental hospital.

Incongruous affect—that is, an emotional response inappropriate to the circumstances—is more commonly seen in later stages of the illness. It needs skilled psychological observation to detect it in an early schizophrenic: it is a sign of great diagnostic value.

IV. Autochthonous Delusions

This symptom ranks first in respect of diagnostic significance among the *positive* symptoms of schizophrenia. It is the fundamental event from which are developed all paranoid schizophrenic states, and is especially noteworthy as the primary experience underlying ideas of reference and other delusions. As it is often cloaked in a secondary elaboration and in features derived from the personality and the environment, a few examples of its pure form may facilitate its recognition.

A patient said: "I went into a café, and there were three white tables; I looked at them, and suddenly I knew that this signified the end of the world." Again, "The clock was at eight; I knew from this that I had to devote myself to religion from now on." "There were red and white suits in the shop-window; this meant that I am of a different descent."

What is characteristic of these occurrences is that out of a casual and commonplace perception a morbid conviction has arisen. This conviction may have a definite content or meaning, or it may be quite vague and indefinite, "something terrible," "something extremely important," etc. It produces, or is perhaps produced by, a peculiar delusional attitude: one might say that the patient is submerged in an atmosphere of misinterpretation. It is unimportant from the diagnostic point of view whether the patient keeps to these delusional ideas or abandons them later on. The building up of a delusional system and the addition of explanation and justification are much less characteristic of schizophrenia than the original autochthonous experience, which in typical cases takes place out of a blue sky. It may be possible by industrious research to discover a connexion between the content of the delusion and previous experience, but this is of little significance. What is important is the readiness to plunge into a mystic conviction, which is beyond all reasoning with. The physician's natural efforts to understand the patient may obstruct his recognition of the morbid character of the delusional experience.

V. Catatonic Symptoms

These anomalies of motor behaviour were regarded as diagnostically specific by Kraepelin when he first created the concept of what to-day we call schizophrenia. They

have lost part of their significance since their frequent occurrence in so-called organic psychoses, especially in states of clouded consciousness, has been observed. Many catatonic features have been seen in encephalitis lethargica and after focal lesions of a like localization. Excitement and stupor in affective psychoses are sometimes indistinguishable from those in schizophrenia. Stereotypies, fixed attitudes, and mannerisms are easily recognized, but they belong as a rule to later stages of the disease.

In early schizophrenia one often finds a rather characteristic pre-stuporose behaviour, a kind of motor constraint lasting for hours or present all the time. To the layman the patients seem drowsy, but they are really not so; they are only as it were restricted in movement and speech. There is often insomnia, and headache is complained of. Others report states of rigidity, which is forced upon them for a short period at night. These akinetic states, and also periods of aimless restlessness, may be split off from everything else in the patient's mind and deprived of any true motivation. Sometimes the patients do not find anything abnormal in their motor peculiarity. A patient awoke from a stupor which lasted over weeks: when questioned why he did not move or speak, he only answered that he felt too bored.

VI. Hallucinations

These can occur in all types of mental illness. Those characteristic of schizophrenia are significant not so much as hallucinations as by virtue of their combination with the symptoms mentioned before—voices reproducing the patient's thought disorder, containing neologisms; bodily sensations closely related to feelings of passivity or to catatonic movements; synaesthesiae with bizarre delusional contents—behind which the hallucination proper remains indiscernible. All these phenomena are relatively rare in early stages of the disease.

It must be remembered, however, that hallucinations in a state of clear consciousness are very common in schizophrenia, but uncommon in other psychoses. Isolated auditory hallucinations are most frequently met with. Commencing schizophrenics often describe phenomena in which they are unable to make a clear distinction between vivid thinking and actual hearing.

The attitude of patients towards their hallucinations is characteristic. Although they can distinguish between the false perception and a real one, they have no insight. Further, though convinced of the reality of their experiences, they may not draw the obvious conclusions or react in an unexpected way. For instance, a man who thought he was perpetually being molested by means of the telephone and the wireless took his complaints not to the Post Office or to the B.B.C., but to a psychiatrist.

Occurrence of Symptoms

Although all the schizophrenic symptoms mentioned in this survey may be found in one patient at the same time or in the course of his illness, many cases show a preference for one or for a small group of these symptoms and never exhibit the others. Thus, some patients develop shallowness of affect and thought disorder, but never have delusions or hallucinations. Some "catatonics" become only stuporose, without any psychological content; they may have a few hallucinations and autochthonous delusions in the introductory stage. There are "paranoids" or "paraphrenics" without demonstrable thought disorder and without disturbances of volition. In other cases the volitional anomalies may entirely predominate in the clinical picture. There is not one among

the main symptoms which cannot be absent in a case of schizophrenia provided the others, or some of the others, are present.

In view of this multiform symptomatology, numerous efforts have been made to establish one of the symptoms as the fundamental disturbance of schizophrenia. Although in each of these theories a certain core of truth is contained, none of them covers the facts with a satisfactory completeness.

General Qualities

There are, however, a few general and structural qualities of the schizophrenic picture which are of diagnostic value. The relative *clearness of consciousness* has been mentioned before. It can be present in states of severe motor excitement, in full-blown hallucinosis, and in deep stupor. The hallucinating schizophrenic who seems completely absorbed in his delusional world, but at the same time notes every detail in his real environment, is the classic example of this psychological picture which has been named "double orientation." It is perhaps not by pure chance that states of disturbance of consciousness like continuous sleep, hypoglycaemic coma, or epileptic fits seem to have some therapeutic effect on schizophrenia.

The *tendency to "splitting"*—that is, a non-systematic psychic disconnexion, from which the name of the illness was taken—is another structural character evident in most cases. Fragmentation may separate ideas from accompanying emotions, mimic expression from proper affect, and speaking from thinking, but also a complex of delusional ideas may be separated from the rest of the personality and emerge only on certain occasions.

It has been said that many schizophrenic symptoms have a quality of peculiar *psychological remoteness from normality*. They are so far from normal understanding that they cannot be described in ordinary language. One cannot imagine what is going on in the patient as one can, to some extent, in all other psychoses. Thus, the reaction of the non-schizophrenic to the schizophrenic can be used as a diagnostic test. At the same time—and this is diagnostically much more significant—the patient himself finds his absurdities not at all strange, but quite natural, rational, and understandable.

As a final general character the *detachment from reality* (Bleuler's "Autismus") has to be mentioned. It often appears as an active withdrawal of the patient from anything that may disturb his delusional world. In later stages of the illness, if favoured by supporting circumstances, it produces a grotesque mental isolation of the patients. In the beginning a detached superiority of the patient to everything that really matters to him may provide the keystone of the diagnosis.

B. Albrigo (*Rif. med.*, 1938, **54**, 1297) records two personal cases of aberrant vaccinia. The first was that of a woman, aged 25, vaccinated in infancy only and the subject of eczema of the vulva, who developed extensive vaccinia of the external genitals, perineum, and anal region. Infection in this case was probably due to her having scratched the eczematous lesions after attending to her recently vaccinated child. Subsequent vaccination on the arm had a negative result. The second case was that of a man, aged 38, who had been vaccinated in infancy and again at 18 years of age and was the subject of peri-anal eczema. The vaccinal nature of the peri-anal lesions in his case was shown by the production of a typical vaccinal keratitis after inoculation of the cornea of a rabbit.

INCIDENCE OF PATHOGENIC STAPHYLOCOCCI IN THE NOSE

BY

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It has been suggested that a factor in the chronicity of some cases of furunculosis and osteomyelitis is the transference of pathogenic staphylococci by the patient's fingers from the nose to the skin or wound. Dolman (1935) found that staphylococci were present in the nose of nine patients with nasal sinusitis and also in the apparently healthy nose of several patients with staphylococcal infections elsewhere. Valentine (1936) obtained cultures of *Staphylococcus aureus* from the healthy nose of fourteen of eighteen cases of chronic furunculosis. In six out of seven of these strains the toxin production (α -haemolysin and Panton-Valentine leucocidin) was comparable to that of the strain isolated from the lesion elsewhere. Apart from the possibility of reinfection of a superficial lesion it is conceivable that pathogenic staphylococci in the nose may sometimes gain access to the blood stream and give rise to an acute osteomyelitis or a perinephric abscess. Thus it is of interest to gain an idea of the incidence of pathogenic staphylococci in the nose of individuals who are free from staphylococcal infection.

Individuals Studied and Methods Employed

During February and March, 1938, nasal swabs were taken from 101 undergraduates aged 18 to 22, thirty-three children in hospital aged 7 months to 16 years, and thirty-one adults in hospital aged 19 to 75 years. None of these had or had recently had a staphylococcal or nasopharyngeal infection.

The nostrils were swabbed through the anterior nares with sterile cotton-wool swabs mounted on a probe. Since the work of Thomson and Hewlett (1895) it has been agreed that, in a healthy nose, cultures from the walls of the nasal cavities proper yield relatively few organisms, while the vestibule, the vibrissae, and crusts of dried secretion yield a plentiful and varied growth (Küster, 1929; Cruickshank and Cruickshank, 1931). From the point of view of a possible source of infection of the patient's fingers it is the vestibule which might be important, so that it is no disadvantage in this investigation that the majority of the organisms obtained on the swabs came from that source.

A swab from each nostril was smeared directly on half an agar plate. The plates were incubated at 37° C. for twenty-four hours. Films were made of suspicious colonies, and when staphylococci were found two or three representative colonies were subcultured into a broth tube. When both *aureus* and *albus* were present colonies of each were examined. The broth cultures were incubated at 37° C. in an atmosphere of 30 per cent. carbon dioxide for forty-eight hours. After centrifugation the supernatant fluid was tested for α -haemolysin by diluting 0.1 c.cm. with 0.4 c.cm. saline, adding 0.5 c.cm. of a 2 per cent. suspension of thrice-washed rabbit red cells and incubating at 37° C. for an hour. A control tube containing 1 unit of antitoxin was set up for each fluid. In a few cases where haemolysis occurred in the control tube, proof that the α -haemolysin was responsible was obtained by showing that the antitoxin neutralized