Turning now to the methods of insertion, it often happens that what we are really constructing is an inserted plaque, when the above rules still apply. This is the case, for example, in the treatment of carcinoma of the breast, where in effect a plaque is formed on the chest wall, or in the treatment of some cases of secondary glands in the neck. In other cases, however, where we are dealing with a localized tumour it is better to regard the problem from a different aspect.

Suppose that we require to treat a spherical mass of growth and that it is possible to distribute our radium both around it and throughout its substance, how should it be distributed and how much should we employ? Again two very simple rules can be formulated. As regards the distribution, arrange one-quarter of the radium uniformly through the growth, and three-quarters just outside its palpable limits—that is to say, just beyond the growing edge. In this way it can be shown that every point of the growth received a nearly equal dose. As regards amount, the number of milligrammes required for a treatment extending over five and a half days or, what is numerically the same, the number of millicuries destroyed—that is to say, the Index—is given by the square of the diameter of the growth in centimetres.

This simple rule depends upon the physical fact that in the case of a sphere such a distribution gives a very uniform irradiation throughout, and at its centre a total irradiation of exactly 6,720 *r* units, whatever the diameter of the sphere may be. For clinical purposes where a tumour is only roughly spherical we obtain a sufficiently accurate result by taking its average diameter.

Comment

It is not, of course, suggested that the rules we have laid down form an infallible guide to radium dosage, or that they can in any way replace experience or the exact calculations of the expert. It is, however, felt that they form standards which even the expert may use as a starting-point, and which he can readily modify to meet any special requirements. The conception of the Index certainly simplifies calculation, and in effect reduces all our problems to a single scale.

The 1938-9 programme of the West London Medico-Chirurgical Society opened on October 7 with the presidential address by Dr. Maurice Shaw on heredity and medicine. Other meetings have been arranged as follows: Friday, November 4, 8.30 p.m., clinico-pathological meeting at West London Hospital. Friday, December 2, 7.45 p.m., at De Vere Hotel, Kensington, W., Discussion: "Illegal Operations." To be opened by Mr. Cecil Binney, Dr. C. P. Blacker, Mr. Aleck W. Bourne, and Dr. W. J. O'Donovan. Friday, January 13, 7.45 p.m., at De Vere Hotel, Discussion: "Some Aspects of Medical Folklore." To be opened by Dr. J. D. Rolleston. Friday, February 3, 8.30 p.m., clinico-pathological meeting at West London Hospital. Friday, March 3, 7.45 p.m., at De Vere Hotel, Discussion: "Pre- and Post-operative Treatment." To be opened by Dr. E. H. Hudson, Mr. Cecil Joll, and Mr. A. Simpson-Smith. Friday, April 14, 7.45 p.m., at De Vere Hotel, Discussion: "Sex Glands in General Practice." To be opened by Professor E. C. Dodds and Dr. L. P. E. Laurent. Friday, May 5, 7.45 p.m., at De Vere Hotel, Discussion: "Some Recent Advances in Medicine." To be opened by Professor Henry Cohen. The Cavendish Lecture will be delivered at Kensington Town Hall on Wednesday, June 7, at 8.30 p.m., and the annual dinner will be held at the Trocadero Restaurant on Wednesday, July 5, at 7.45 p.m.

THE ANTI-PERNICIOUS PRINCIPLE: SOME EXPERIMENTS WITH URINE

BY

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We have no proof that the anti-pernicious principle circulates in the blood, although some authors explain in this manner the partial efficacy of blood transfusions in pernicious anaemia. Its presence in organs other than the liver cannot be deduced from the experiments of Whipple and Robscheit-Robbins (1925), which established that the haematopoietic power of the kidneys, for example, is equal to that of the liver, that of the brain one-third as great, etc. The experiments of Whipple were based upon the rate of blood regeneration in dogs exsanguinated by successive haemorrhages, and in no way prove the presence of *anti-pernicious* principle in the organs concerned. It remained for Minot and Murphy to apply clinically the discoveries of Whipple and to show that pernicious anaemia was peculiarly responsive to the action of liver. Furthermore, since the introduction of therapeutic extracts (Cohn, McMeekin, and Minot, 1930) of increasing purity it has become possible to distinguish the specific action due to anti-pernicious principle from that which causes blood regeneration in non-pernicious anaemia and is due to other haematopoietic substances (Farrar and Sturgis, 1936; de Jong, 1938).

The presence of an anti-pernicious principle has, however, been demonstrated in the kidneys (McCann, 1928), the lungs (Hitzenberger, 1934), the brain, salivary glands, and pancreas (Dakin, Ungley, and West, 1936), and the saliva (Tempka, 1936). This substance, as emphasized by Wakerlin (1937), cannot be precisely identified with that of the liver, since the methods employed in preparing active extracts of liver are ineffective when applied to other organs.

Briefly, although we are in the realms of hypothesis, it would not appear unlikely that the anti-pernicious principle, widely diffused throughout the body and present in the kidneys, should be eliminated, like so many hormones, in the urine. In 1935 Wakerlin reported favourable results from the treatment of pernicious anaemia by intramuscular injections of a concentrated extract of normal urine, while Decastello (1935) obtained similar results with urine administered both by injection and per rectum. Wakerlin, however, in a more recent work (1936), based upon a greater number of cases, was unable to confirm his previous results.

The confirmation of such a fact as the presence of an active anti-pernicious principle in normal urine would not only possess a considerable theoretical interest—in establishing that the metabolism of the principle is not confined to the alimentary tract and liver—but would have a practical application in suggesting the elaboration of a method of biological diagnosis of pernicious anaemia based upon the absence of anti-pernicious principle from the urine. It is for this reason that the experiments to be described were attempted.

Choice of Method

The fact that pernicious anaemia does not occur in animals greatly limits our means, since animal experiments do not enable us to distinguish between a simple haematopoietic action and a specific anti-pernicious action. Such experiments have been far from valueless, since it was by their means that Whipple succeeded in demonstrating the therapeutic properties of liver; yet the interpretation of their results may lead to errors which can only be avoided by clinical control. Within certain limits, however, they may be employed to supplement the scarcity of cases of pernicious anaemia suitable for subsection to long and complicated investigations. (The difficulties of purely clinical experimentation explain the somewhat slow progress which has attended the study of everything touching upon the anti-pernicious principle.) Various methods have been used for such experiments, all of which consist in observing the action of the substance under investigation either upon anaemia or upon the reticulocyte content of the blood of certain animals: space forbids their enumeration here.

The method chosen in the present instance was that depending upon reticulocyte reaction in the white rat. Introduced by Singer (1932), it has been employed by numerous others (Fleischhacker and Schlesinger, 1935; Kamerling, 1935; Baráth and Fülöp, 1935; Leiner, 1935; Feigin and Plonskier, 1936; Crosetti, Bajardi, and Margulius, 1937; Levi, 1937; Mark and Hauke, 1937); and, with certain differences of technique as previously described by one of us (Jéquier, 1936), has been in use for the past three years at the Lausanne medical clinic. Its details will not be recapitulated here.

The following table shows the results obtained with normal urines.

No. of Tests	Test Material	Result		
		Positive	Negative	Doubtful
10	Normal urine, untreated ..	7	1	2
10	Normal urine, concentrated* ..	10	—	—
10	Normal urine, heated† ..	10	—	—

* Concentrated to half its volume by evaporation *in vacuo* at laboratory temperature, as the animals appeared insufficiently sensitive to small quantities of urine.

† Heated to boiling point for ten minutes to destroy the thermolabile fraction of the anti-pernicious principle.

Owing to the comparative rarity with which untreated cases of pernicious anaemia are now seen at the clinic it was possible to obtain for experimental purposes only four such cases. All four presented a complete clinical picture with the characteristic triad—typical blood picture, disorder of the alimentary tract (glossitis, gastric anacidity, tendency to anorexia and diarrhoea, etc.), and disorder of the nervous system; the latter was especially marked in one case which showed typical pseudo-tapes.

The haematological abnormalities were studied not only in the peripheral blood, which revealed intense hyperchromic anaemia with leucopenia and thrombopenia, but also in the bone marrow obtained by sternal puncture. The latter showed inhibition of cellular maturation with predominance of young forms, of which the greater number were megaloblasts as described by Naegeli (1936). In all four cases the blood state was restored to normal by the administration of liver extract.

In each case, before the inception of treatment, a subcutaneous injection of 3 to 5 c.cm. of urine which had been concentrated to half its volume provoked a positive reticulocyte reaction in the white rat. The details of these

reactions, together with those of reactions obtained with one specimen of normal urine, are set forth in the following table.

Table showing Details of Reactions following Injection of Urine in White Rats

Urine	Number of Reticulocytes per 1,000 Red Cells						
	Before Injection		After Injection				
	Day 1	Day 2	Day 1	Day 2	Day 3	Day 4	Day 5
Normal	11	9	12	27	30		
" concentrated ..	15	18	16	35	19		
" heated	18	11	14	16	14	39	
Pernicious anaemia (Mme W. H.) ..	16	23		22	30	38	25
" "	11	10		25	39	14	13
Pernicious anaemia (Mme S.) ..	6	7		31	40		
" "	10	9		36	45		
Pernicious anaemia (Mme P.) ..	7	5		11	31	29	
" "	11	13		10	29	35	
Pernicious anaemia (Mme P. A.) ..	5	8		11	28	40	
" "	14	16		12	41	30	

Conclusions from the Above Experiments

The urine of untreated cases of pernicious anaemia contains, like normal urine, a substance capable of provoking a reticulocyte reaction in the white rat. It may be assumed that this substance is not the anti-pernicious principle of liver, the presence of which could hardly be conceived in such cases; its existence nevertheless precludes the utilization of the present method as a means of demonstrating the absence of that principle. The results obtained are in contradiction to those of Leiner (1935), who found that untreated cases gave a negative reaction which became positive after specific treatment was instituted.

Although it appears that the positive reactions reported above were due to a substance other than the anti-pernicious principle, the possibility remains that the urine of healthy persons may contain this principle. The proof of such a hypothesis would be at least of interest with regard to the metabolism of the principle, and for this reason the clinical investigation now to be described was made.

Clinical Experiment

This experiment was carried out upon one of the four patients previously mentioned (Mme W. H.).

A daily blood count showed a constant level of between 10 and 15 reticulocytes per 1,000 red cells; there was thus no tendency to spontaneous amelioration. The haemoglobin was 58 per cent., the red cells 1,820,000, and white cells 4,000 per c.mm.

From January 24 to 28, 1938, the patient received, after going to stool, a drop-by-drop rectal infusion of 300 to 500 c.cm. of normal urine, specific gravity above 1020, filtered through paper, coloured with Congo red (one drop per 100 c.cm.) and warmed to body temperature. (Decastello in his experiments decolorized and deodorized the urine by filtration through animal charcoal. As this procedure lowers the specific gravity of the fluid to a considerable degree, it was feared that the principle under investigation might be retained by the filter, and filtration through charcoal was therefore omitted.) The first two infusions were well tolerated, but the ensuing ones provoked colic and diarrhoea. It is therefore probable that the urine was not completely absorbed by the intestine. The addition of tincture of opium did not prevent these manifestations.

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.

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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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