urinary tract. In the other case *E. coli* was found, as had occurred in the earlier sample. Repeated culture gave a negative result. The patient had, however, received sulpha preparations continuously.

Discussion

The first question in the assessment of a test for the determination of urine erythrocytes and leucocytes is whether it is sensitive enough. Normal urine is thought to contain a maximum of some 20 red cells per c.mm. For normal adult males the content is no more than two red cells per c.mm. (Larcom and Carter, 1948). Watson-Williams (1955) estimated the red-cell content to be about 10 times as great in women. The P.A. test was either 0 or 1 mm. if the quantity of red cells in question was 25 or fewer per c.mm. A larger red-cell count invariably gave a higher reading. With regard to erythrocytes, then, the P.A. test can be regarded as sensitive enough to indicate pathological amounts of red cells in urine. The value 0 mm. is negative, 1 mm. is uncertainly positive, 2 mm. and over positive. The reading gives a sufficiently good idea also of the quantity of red cells. As regards leucocytes, the same conclusions are warranted on the basis of the tests performed (Tables II and III). Normally fewer than 10 leucocytes are present per c.mm. of urine (Dukes, 1939). Five leucocytes per c.mm. gave a P.A. reading of 0 mm.; when there were 20 leucocytes per c.mm. the reading was 5 mm.

A weak point, of course, is that the test does not differentiate between erythrocytes and leucocytes, which still has to be done by microscopy. As already pointed out, haemoglobin also gives a positive reaction, since it contains peroxidase. This weakness notwithstanding, I find it suitable for routine examination on account of its simplicity and reliability. Opinions may naturally differ over the necessity for routine urine examination for erythrocytes and leucocytes. However, infections of the urinary tract alone are so common, especially in women, that some such examination seems necessary. Halonen and Halonen (1950) found these infections in 13.1% of female hospital patients. In two Amsterdam hospitals the figure was 29% (Loopuyt, 1946). Jäämeri (1943) found in 600 pregnant or puerperal women that 29% in pregnancy and 21% in puerperium had an infection of the urinary tract. The early diagnosis of this infection has an added importance to-day, when the facilities for its treatment are better than before. Only thus is it possible to avoid the development of numerous cases of nephrocirrhosis pyelonephritica.

The procedure in the P.A. test was arrived at empirically. Great emphasis was laid on making even moderately pathological amounts of red cells and leucocytes in urine give the strongest possible peroxidase reaction. For instance, hydrogen peroxide solutions were experimented with in 3, 10, and 30% dilutions. The quantities used in the tests varied from 1 drop to 2 ml. Although 4 drops of 30% hydrogen peroxide was finally decided upon, it was observed that 3-7 drops gave nearly the same result. Actually this means that the urine sample taken in the small tube need not be measured with particular accuracy. Thirty minutes was established, also empirically, for the reading of the P.A. value. A further increase in the value often occurred between 30 and 60 minutes, but it was slight. The maximum was often reached before 30 minutes: in fact, the qualitative and to some extent even the quantitative result can be indicated within some 20 seconds of taking the sample into the tube. The formation of gas bubbles in the tube points to the presence of an increased amount of peroxidase, and the rate of bubble formation is in relation to its quantity. In 20 seconds 50 red cells per c.mm. have already produced a distinct bubble formation.

Clearly, a more accurate result would be possible in peroxidase determinations if the volume of gas given off could be ascertained more exactly. Indeed, it is obvious that when the above procedure is used the quality of the urine—for instance, surface tension—affects the result, as was shown in Table I. The amount of gas given off was easy

to determine in the tube apparatus employed in the sugar fermentation test. Greater stress was laid, however, on simplicity of method than on small gains in accuracy.

Summary

A simple method has been evolved for the preliminary determination of the quantity of erythrocytes and leucocytes in urine. The amount of peroxidase contained in erythrocytes and leucocytes (haemoglobin) was estimated with an ordinary E.S.R. apparatus. The only reagent needed was 30% hydrogen peroxide. The accuracy of the method was assessed as satisfactory for the practical requirements of clinical work.

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CARBUTAMIDE IN TREATMENT OF SCHIZOPHRENIA*

BY

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Carbutamide (BZ.55), appearing to act as a euphorizing anti-hallucinogen, has given encouraging results in the treatment of 60 patients with schizophrenic illness, 45 of whom left the mental hospital recovered or relieved. The drug was originally introduced by Achelis and Hardebeck (1955) as an oral hypoglycaemic substitute for insulin in the treatment of diabetes, and was known to produce euphoria in normal healthy subjects (Franke and Fuchs, 1955).

I have already described a tentative application of carbutamide to psychiatric cases (Frost, 1957), and the present communication gives substance to the value of this drug as an anti-hallucinogen in schizophrenia.

Administration.—On the first day—a test day—a fasting blood-sugar is estimated; three 0.5-g. carbutamide tablets are given and the patient takes no food for one hour, when a further blood specimen is withdrawn for glucose estimation. The patient is then given food and glucose. Three 0.5-g. carbutamide tablets are thereafter given for not more than three successive days a week, followed by a drug-free interval of four days. This regime is repeated for four weeks only. Except on the first test day, the tablets are given with $\frac{1}{2}$ –1 oz. (14–28 g.) of glucose in a drink of water or mineral water, and the patients are encouraged to take glucose *ad lib.* throughout every day of the course and for two weeks after. *The hypoglycaemic effect of the carbutamide is to be avoided during treatment.* Patients should be kept under hospital observation for two weeks after the end of the course.

Results

Of 60 patients, 45 were discharged recovered or relieved. Of seven subsequently readmitted, four left hospital again after a second, shorter, course of carbutamide.

*Based on a paper read to the second International Congress for Psychiatry, Zurich, September, 1957.

In schizophrenic illness superimposed upon mental defect or intellectual retardation the psychotic episode was cut short and restoration to home life effected. Hallucinoses could fade quickly, sometimes in a few days, or could linger till the end of the course; depression would lift in a rather more steadily progressive manner, and was often replaced in the third week of treatment by euphoria. Of poor prognostic omen were agitation and tension in the schizo-affective cases, and, of course, obsessive cases did not do well. If the blood-sugar level rose instead of falling as expected on the first test day the outlook was ominous. No death occurred in this series.

Two groups of cases were covered: group 1 consisted of first admissions treated by carbutamide alone (30 cases); group 2 consisted of 30 cases treated by drastic physical methods (deep insulin coma in 17 and E.C.T. in 13) in a previous or during the present admission before recourse was had to carbutamide. In group 1 (naturally the most recent cases with shorter histories) 26 were alleviated; in group 2, 19 improved.

In this study, 54 cases had less than a 12-months history: in six instances attacks had occurred two to six years previously. Table I gives a summary of the clinical groups concerned.

TABLE I

Diagnostic Groups of Schizophrenia	No. of Cases	Recovered	Relieved	Not Improved
Simple hebephrenic ..	20	9	5	6
With mental defect ..	4 } 8		4 } 8	
With backwardness ..	4 }		4 }	
Paranoid states ..	11	4	4	3
"Schizo-affective" ..	15	8	4	3
With obsessive features ..	6		3	3
Totals ..	60	21	24	15

Teenage Hebephrenes.—Of seven teenage hebephrenes, five did well on carbutamide. All exhibited hallucinosis, fatuity, suicidal behaviour, and neglect of the person. These five lost their hallucinations, were no longer suicidal, spoke relevantly, and departed neat and presentable youths. One left to resume grammar-school study; another has taken up decorating work; a third certified patient, who "escaped" from hospital, absconded from home (the parents not knowing his whereabouts), but managed to find himself work, saved £80 in two months, and returned safely to his family, welcomed as warmly as any prodigal son.

Mental Defectives with Superimposed Schizophrenic Illness.—Four cases in this series were mentally defective. Aural hallucinosis was coupled with unemployability in all cases; one was apprehensive, and another was excited and aggressively impulsive. In addition there were four dull intellectually backward patients in whom a schizophrenic illness was successfully treated. All, defective and retarded, went home relieved.

Paranoid Cases; Psychotherapeutic Openings.—Carbutamide renders paranoid schizophrenics accessible to psychotherapy in a state of clear consciousness untrammelled by hallucinosis, depression, or though blocking. Hallucinoses might go, but a suspicious frame of mind could persist. In one case a Nigerian male nurse was asked, as were all the staff, about 30s. missed by a patient. The nurse thought accusations of theft were being levelled particularly against him, even though the money was found in half an hour in the patient's discarded linen. The nurse thought someone else had placed the money to spare the nurse's conviction. An acute schizophrenic reaction followed with accusatory hallucinosis and fear of death. The acute phase passed quickly with carbutamide therapy. The nurse resumed his nursing work, but suspected that he was being supervised and was not being given sole charge because he had been in a mental hospital. But he could see the possibility that perhaps a "cautious" policy was explicable in the light of his mental breakdown—and, for the first time, faced the issue

of going back home as a solution hitherto precluded on grounds of pride and "face-saving."

Toxicity Tests and Precautionary Measures

Agranulocytosis, thrombocytopenia, and a toxic effect on the liver were the risks most feared by those who used carbutamide for its oral hypoglycaemic effect in diabetes. Therefore counts were routinely made of white cells and thrombocytes; also a liver turbidity test.

In this series no death occurred; no leucopenia; and in only two cases was there a temporary drop in the thrombocyte count.

TABLE II.—Correlation Between Serum Sulphonamide and Blood-sugar Levels

	Case 1	Case 2	Case 3
Total serum carbutamide (mg./100 ml.)	24.2	27.2	29.0
Free (mg./100 ml.)	12.1	10.9	11.7
Bound	12.1	16.3	17.3
Fasting blood sugar (mg./100 ml.)	73	61	65
1 hour after carbutamide (mg./100 ml.)	45	42	34
1½ hours	42	38	34
2	45	68	38

As glucose was given freely throughout treatment, hypoglycaemic reactions were slight (sweating, giddiness), and only occasionally was it necessary to give it intravenously (10–20 ml. of 50% glucose sufficed).

Barbiturates were forbidden, lest the risk of agranulocytosis was increased. Bone-marrow soup was given daily as a prophylactic against agranulocytosis.

Three illustrative cases are reported. The correlation between serum sulphonamide and blood-sugar levels is shown in Table II.

Case 7

A boy aged 15 (school leaver) was admitted to hospital on October 24, 1956. On admission he was neglected and unkempt. His conversation was disconnected. His mind, he stated, was muddled and confused. He had thoughts of taking his life. He said, "I shall cease to live." He heard voices of men and of women. He wept. Genetically loaded: mother certified. He was given tranquillizers; electric convulsion treatments (17); also deep-insulin-coma therapy. He was incontinent, salivated, and held his food in his mouth without chewing. Later he began to refuse food. He was found sitting in a washbowl masturbating, with his feet in another washbowl. Owing to risk of malnutrition and its effects, the carbutamide was given with glucose in the tube feed.

On January 31, 1957, he was no better, and carbutamide was discontinued. Electric convulsion treatment was recommenced—six were given between February 1 and 18. He improved slightly, only to relapse on March 15 with hallucinations.

On March 25 carbutamide with glucose was given. He responded well, lost his hallucinations, spoke relevantly, and began to occupy himself. He left hospital on April 17 and took a job. When seen on a follow-up visit he had clearly "recovered." W.B.C., 7,600/c.mm.; thrombocytes, 214,000; thymol turbidity, less than 1 unit.

Case 8

A male student aged 17 was first admitted to Deva Hospital on August 3, 1956, mute, resistive, and uncooperative. He showed mannerisms and grimaced. He heard noises in the head and a voice. He made sudden dashes, only to stop suddenly, standing in a fixed position. E.C.T. and deep insulin coma gave no benefit. He departed, "not improved," on November 7. Diagnosis, schizophrenia.

He was certified on December 6, being manneristic; he grimaced, made fatuous remarks, and was aggressive. Tranquillizers had little effect. He subsequently escaped twice,

to be brought back. Psychological report on December 24: verbal I.Q., 108; performance I.Q., 92; full-scale I.Q., 101 (Wechsler Bellevue Scale).

Mental deterioration: a net loss 11%—Rabin's ratio. Giggled and grimaced. Was listless, retarded, bizarre, had difficulty in verbalizing, and lacked insight. His M.M.P.I. T score for schizophrenia was 96, indicating a fairly advanced cluster of schizophrenic symptoms.

On March 18, 1957, his fasting blood sugar was 80 mg./100 ml.; one hour after the drug it was 68 mg./100 ml. Carbutamide was given; his behaviour improved, he began to show insight, and lost his mannerisms. He became occupied, but while on leave he absconded altogether and was discharged by escape on August 5. Two months later he returned home, having by his own labour saved £80. He said he had gone away to prove that he could fend for himself.

Case 9

A youth aged 17 was admitted as a voluntary patient on September 16, 1957. He had previously been a patient for two weeks in February, 1957, and been given E.C.T.

On admission on the second occasion he was extremely frightened. He also cried and laughed irrelevantly, and seemed to be preoccupied, in a listening attitude, with auditory hallucinatory experiences. A duly authorized officer reported on February 6 that the patient had never made progress at school, and over the past two months had made references to the people on television, sitting in a corner.

Psychologist's report on September 18: verbal I.Q., 61; performance I.Q., 60; full-scale I.Q., 60 (mental defective) (Wechsler Bellevue Scale). A further report on October 17 showed: verbal I.Q., 57; performance I.Q., 64; full-scale I.Q., 60 (mental defective). He made some effort in direct-stimulus response situations, but failed where conceptual thinking was required. On November 11 the report was: verbal I.Q., 73; performance I.Q., 90; full-scale I.Q., 79 (less 10% practice effects, 71—borderline). He was reassessed on a new scale—the Wechsler adult intelligence scale. The validity was checked by the administration of the progressive matrices (Grade V=intellectually defective). He would be capable of working only in a non-competitive environment under supervision.

On September 23 his fasting blood sugar was 90 mg./100 ml. One hour after the drug it was 80 mg./100 ml. On October 8 the W.B.C. was 7,600/c.mm.; thrombocytes, 357,000/c.mm.; thymol turbidity, less than 1 unit.

The diagnosis in this case was a schizophrenic illness superimposed upon mental defect. He was placed on carbutamide and the schizophrenic illness responded well; he lost his hallucinations and fear, and was able to work to the full limits of his limited intelligence. There is every hope that a place will be found for him at a Remploy factory.

Summary

Of 60 schizophrenic patients treated with carbutamide, 45 were sent home recovered or relieved. Carbutamide has proved a safe drug when used for four weeks with drug-free intervals. No death occurred in this series.

I acknowledge the help of Mr. H. V. Ridpath, who carried out the routine laboratory sugar and sulphonamide estimations and toxicity tests; the observation and care of the nursing staff, and Charge Nurse R. Lawson in particular; the general advice given by Dr. A. Grünbaum, whose experience of carbutamide at his diabetic clinic made me cautious about the toxic hazards. I thank the late Dr. L. J. Draspa for the results of clinical psychological assessments, and Messrs. Eli Lilly and Company for supplies of carbutamide freely given.

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Medical Memoranda

Case of Tuberculous Rheumatism

An association between tuberculosis and some forms of rheumatism has been much canvassed on the Continent since the work of Poncet at the turn of the century (see Poncet and Leriche, 1909). The literature has been reviewed by Brav and Hench (1934) and Hammes (1951). In Britain and America "tuberculous rheumatism" has never been generally accepted as an entity, and Brav and Hench (1934), who add a statistical and pathological study of their own to a critical review of the literature, consider that no unequivocal proof has ever been produced for the existence of such a disease. Sheldon (1946) says: "There can be no doubt that such cases [of tuberculous rheumatism] exist . . . although cases reported in English writings are so rare that the condition in this country must be either very uncommon or possibly overlooked." He reports six cases, all in children, seen in eight years, and refers to three cases reported by Findlay in 1920, also in children. Dalglish (1952) reported a doubtful case. This paucity of cases in the English literature prompts me to record the following history.

CASE REPORT

In January, 1956, a pilot then aged 25 had a small haemoptysis. At about the same time he developed a rash on both legs which was ultimately diagnosed as a papulo-necrotic tuberculide. A few days after the haemoptysis he complained of pain and stiffness in the right ankle, followed by similar symptoms in the left ankle after another two days. He also noticed at this time a swelling in the left side of his neck. On February 6 the positive clinical findings were the rash, enlargement of glands below the left mandible, effusions into both knees, and swelling and stiffness of both ankles. Chest x-ray examination showed no abnormality, the E.S.R. was 23 mm. in one hour, and the Mantoux reaction was positive at 1/10,000. On bed rest and large doses of aspirin his symptoms disappeared and his joints returned to normal in one week. Two weeks after the beginning of treatment his E.S.R. was 6 mm. in one hour and the aspirin was stopped.

In April a sterile left cervical abscess was drained; biopsy of the abscess wall showed no diagnostic features, and no tubercle bacilli were seen on direct smear of the pus. Tonsillectomy was carried out in May.

Apart from his rash, which persisted, he remained well until February, 1957, when a swelling developed above the left clavicle. This was excised, and found to be a caseating tuberculous gland. Late in June he developed right-sided pleuritic pain and a mild pyrexia. Chest x-ray examination then showed a small right pleural effusion. He was admitted to hospital six days later, by which time he was symptom-free and afebrile, and x-ray examination showed complete disappearance of the effusion, with clear lung fields. The tuberculide was present on both legs, and he had crepitus in both knees. The E.S.R. was 2 mm. in one hour, x-ray films of the knees and ankles showed no abnormality, and biopsy of the parietal pleura on the right showed non-specific fibrous thickening.

COMMENT

This man shows a picture of prolonged yet essentially benign tuberculous involvement of lymph nodes and skin, associated with two episodes of fleeting inflammation of serous membranes, once in the knees and ankles and once in the pleura. No doubt many of the reports on "tuberculous rheumatism" deal with cases of frank tuberculous arthritis, or else with acute rheumatic fever or rheumatoid arthritis coincident with tuberculosis elsewhere in the body. Sheldon (1946) maintains that there remains a core of cases in which fleeting rheumatic symptoms and signs are intimately associated in time with acute tuberculosis elsewhere in the body. He emphasizes that such joint involvement is found on close analysis to be unlike that of acute rheumatic