intermittently. The immediate cause of death was heart failure, although the clinical symptoms suggested overdosage of one or other of the antidepressant drugs. Analysis showed no evidence of overdosage, and the conclusion that the combined drugs taken in substantially normal dosages had produced these symptoms and contributed to her death seems a more reasonable explanation than that put forward by Dr. Sargent. Surely such a patient can be hypersensitive to the newly introduced drug (desipramine) in combination with the drug (phenelzine) which she has tolerated for so long. With all due respect to Dr. Sargent, the fact that previously she had shown no adverse reaction to a different drug (amitriptyline) in combination with phenelzine seems irrelevant to me.

It may well be that cases like this are extremely infrequent, but need one therefore deny that a small risk exists? If the probable benefit to the patient is greatly in excess of the small risk, then experienced psychiatrists like Dr. Sargent are presumably justified in using this line of treatment without fear of litigation. Those with less specialized experience in using antidepressant drugs will probably prefer to heed the warnings of the Witts Committee and other authorities. One such authority, Dr. Hollister, writing on "The Toxicity of Psychotherapeutic Drugs" in the current *Practitioner*,¹ states that "Any such combination is far too dangerous for general clinical use."—I am, etc.,

G. F. M. HALL.

Department of Pathology,
General Hospital,
Nottingham.

REFERENCE

- ¹ Hollister, L. E., *Practitioner*, 1965, **194**, 72.

SIR,—A high proportion of patients with a depressive illness will respond to an antidepressant drug or, if refractory, electroconvulsive therapy. But a small number will either not respond at all or quickly relapse. It is in these patients that combined antidepressant therapy is sometimes remarkably effective.

Eight of my patients are at present receiving a combination of amitriptyline (150 mg. a day) and either iproniazid (Marsilid) (50–100 mg. a day) or isocarboxazide (Marplan) (20–30 mg. a day). All have been seriously disabled by their symptoms continuously for between two to seven years and have failed to respond to antidepressant drugs given alone or combined with tranquillizers and/or E.C.T. The severity of their symptoms is reflected in the fact that one has had a modified prefrontal leucotomy and three others have been considered for this operation. All have at some time during their illness contemplated the possibility of suicide. All these patients are now sufficiently well to be able to work and again lead useful lives. Their symptoms are suppressed rather than cured, as with all antidepressant drugs, and attempts to stop or reduce the dosage of one or both of these drugs result in symptoms returning.

No one will deny that combinations of antidepressant drugs are liable to show side-effects and sometimes to bring about signs of marked over-stimulation. But I suspect that amitriptyline is much safer in this respect than imipramine (Tofranil), just as the hydrazine monoamine-oxidase inhibitors

are probably safer than tranlylcypromine (Parnate). This may be related to the fact that amitriptyline has, on the whole, more of a sedative and less of a stimulant action than imipramine. Like Dr. Sargent (23 January, p. 251) I have seen no serious side-effects from combining iproniazid or isocarboxazide with amitriptyline, although excessive weight gain, incoordination, and hypotensive effects may require dosages to be reduced. To the best of my knowledge no deaths, apart from those due to suicidal overdosage, have been reported, in contrast to when imipramine is combined with an M.A.O.I.

As Dr. Rees and Dr. Pare¹ emphasized recently, it is often misleading to consider drugs of the same class as exhibiting similar toxic effects and potentiating activities, since each drug has its individual characteristics. This surely needs to be applied here. The combination of amitriptyline with an M.A.O.I. can be extremely effective, and it would, in my view, be wrong to condemn this treatment on what appears to be emotional rather than scientific grounds.—I am, etc.,

Department of Psychological Medicine,
Westminster Hospital,
London S.W.1. P. J. DALLY.

REFERENCE

- ¹ Rees, L., and Pare, C. M. B., *Lancet*, 1963, **2**, 1279.

SIR,—The indications and risks of combining the antidepressant drugs were discussed and put into perspective at a symposium held at St. Bartholomew's Hospital recently.¹

Combining the two groups of antidepressants clearly increases the risk of side-effects. On the other hand, this risk is minimized if they are given by physicians experienced in the use of antidepressants and thoroughly acquainted with their pharmacology. In such hands the increased incidence of side-effects is often justified in severely depressed and otherwise resistant patients because of the clearly increased antidepressant effect of the drugs in combination.—I am, etc.,

C. M. B. PARE.

Department of Psychological Medicine,
Saint Bartholomew's Hospital,
London E.C.1.

REFERENCE

- ¹ *Scientific Basis of Drug Treatment in Psychiatry*, 1965, in press.

SIR,—For the last 13 years I have been treating a lady, now aged 51, for a depressive illness. During this time she has had two hospital admissions, five courses of E.C.T., as well as a trial of almost every new antidepressant drug as these became available. Her psychiatrist stopped her last course of E.C.T. in February 1964. She was no better. In desperation, and encouraged by the writings of Dr. William Sargent, I began to treat her cautiously with a combination of Parstelin (tranlylcypromine and trifluoperazine) and Tofranil (imipramine) in February 1964. Although she has not fully recovered she is, almost a year after this treatment was started, in her own words "tons better." Whereas previously I had been sent for frequently because she felt so

awful she now comes to see me about once a month for a check-up and an adjustment of dosage.

I wonder, Sir, whether those who condemn these very useful drugs and the very occasional need to combine them really have to bear the everyday, year-after-year burden of looking after these patients?—I am, etc.,

Sheffield 2.

H. M. HALLE.

Diagnosis of Amphetamine Addiction

SIR,—I read this letter (2 January, p. 57) with special interest, as in this area of Lanarkshire we find the problem of drug dependence a chronic and continuing one. While numerically the numbers of patients involved is small they do cause a quite disproportionate degree of irritation to both the police and the hospitals by their activities. While we do not seem to have any organized traffic in these drugs a small number of "problem" families undoubtedly overindulge to the extent of producing psychotic and antisocial behaviour.

Could I make the point that it must be rare indeed to encounter an amphetamine user in pure culture? In my experience the picture is almost always blurred by a concurrent barbiturate dependence—usually one of the short-acting variety. Doubtless this is taken to modify the unwanted and unpleasant somatic symptoms of tremor, sweating, etc., produced by excessive doses of sympathomimetic substances. In view of this would it not be better to refer to the condition as amphetamine/barbiturate addiction—the more so when one remembers the quite clear-cut type of dependence that the two drugs produce.¹

I am afraid I have not seen the changes in the buccal mucosa as described, nor am I happy about the allegedly diagnostic chewing movement. In any tense and anxious person habits of chewing, teeth grinding, and licking of the lips are so common as to make the presence or absence of these signs of no value whatever in diagnosis of a toxic psychosis of such a subtle type as these drugs produce. And are the signs in rabbits of any real value?

To make a tentative diagnosis of a drug intoxication in the surgery or out-patients department is very much a clinical problem and is like the recognition of early schizophrenia a matter of a *general impression* coupled with a largely subconscious awareness of the differential diagnoses. While this may sound rather crude by the standards of pure science I am sure that it is the only approach to the problem, and that to search for physical signs of very doubtful validity will only at this point confuse the clinician further.

Amphetamine/barbiturate addicts are as unreliable as any when it comes to admitting their activities, and I would be very suspicious of the confident statement that "When confronted with this evidence they usually 'come clean.'" A positive diagnosis is really impractical unless biochemical facilities of above average are available for examination of urine specimens. Connell² has summed up the position well, but even the simplest and shortest methods he describes are pretty exacting in time, equipment, and most of all experience in the laboratory technician. From

my own experience a request for the estimation of amphetamine in urine is disconcerting to the biochemistry department of even major teaching hospitals and quite beyond the capacity and experience of most other laboratories.

I would be very interested to hear the feelings of psychiatrists about these points.—I am, etc.,

PATRICK G. M. G. WALKER.

Hartwood Hospital,
Lanarkshire.

REFERENCES

- ¹ *Wild Hlth Org. techn. Rep. Ser.*, 1964, 287.
- ² Connell, P. H., *Amphetamine Psychosis*, Maudsley Monograph No. 5, 1958. Part 2.

Rapid Estimation of Urea

SIR,—I was interested in the paper by Professor D. N. Baron and Dr. Gwilym Hughes (23 January, p. 233). From general practice my limited experience of Urastrat (see Table) encourages me to believe that this is a useful addition to the expanding range of simple biochemical tests.

Serum-urea Nitrogen on Same Samples of Blood

Patient	AutoAnalyzer (Expressed as Urea Nitrogen, mg./100 ml.)	Urastrat (mg./100 ml.)
1	10	17.5
2	11.6	15
3	14	13.8
4	17	18.8
5	25	22.5
6	27	27.5
7	29	25

By eliminating the need for centrifuge—or waiting for the blood clot to retract sufficiently—Baron and Hughes have brought this technique well within the capacity of the busy family doctor.

I wish to thank Dr. S. L. Tompsett, Biochemist, Northern General Hospital, Edinburgh, for the AutoAnalyzer results.

—I am etc.,

Edinburgh 5.

J. D. E. KNOX.

Folic-acid Deficiency in Pregnancy

SIR,—In your annotation "Lettuce for Mothers" (9 January, p. 75) you state that the most likely explanation of incipient deficiency of folic acid is that this substance has to be provided for the developing foetus. We should like to put on record the following case report which throws an interesting light on the mechanism of folic-acid deficiency in pregnancy.

A 23-year-old Indian, resident in this country for the past several years, became pregnant in February 1964. Her previous two pregnancies were normal. At the 32nd week her haemoglobin was 8.6 g./100 ml., and numerous macrocytes were present in the peripheral blood film. Oral administration of folic acid (10 mg. twice daily) was commenced. Six weeks later her haemoglobin was still 8.6 g./100 ml. Bone-marrow biopsy showed megaloblastic erythropoiesis. Her serum-vitamin-B₁₂ level (*Euglena-gracilis* method) was 280 µg./ml. and serum folate (*Lactobacillus-casei* method) 3.2 mµg./ml. In view of these findings oral folic acid was continued. There was a marked response in the 40th week, her reticulocyte count rising to 19%. A normal delivery occurred in the 42nd week and

at this time the haemoglobin and folate levels in mother and infant were:

Mother: haemoglobin 11 g. per 100 ml.; serum folate 2.5 mµg./ml.

Infant (cord blood): haemoglobin 16.8 g. per 100 ml.; serum folate 10 mµg./ml.

Three weeks later the mother's haemoglobin had risen to 14.2 g. per 100 ml.

More work is needed before a firm conclusion can be drawn from this, but the discrepancy between maternal and foetal levels of serum folate is suggestive of a unidirectional transfer of folic acid across the placenta resulting in probable interference with utilization of folic acid for maternal haemopoiesis. The sudden reticulocytosis in the 40th week suggests a reversal of folic acid transfer towards the mother.—We are, etc.,

A. K. SINGH.

N. K. SHINTON.

Coventry and Warwickshire Hospital,
Coventry.

Iron-deficiency Anaemia in Infancy

SIR,—Dr. James Grant (16 January, p. 193) is right to draw attention to the commonest nutritional disturbance of infancy now occurring in this country—namely, iron deficiency. The incidence of iron-deficiency anaemia in infants is not known but undoubtedly it is common. During the past 2½ months of 70 infants and children less than 3 years old admitted to one ward of an acute children's hospital 32 (45.7%) had a haemoglobin of 10.5 g./100 ml. or less, and of these 23 (33%) had less than 10 g./100 ml. Excluding those infants who were less than 6 months old (when iron deficiency is less likely to be the cause of anaemia), 26 out of 45 (57.7%) had a haemoglobin of less than 10.5 g./100 ml. and in 19 of these (42%) it was less than 10 g./100 ml. Although the anaemia was not fully investigated a stained film in nearly every case showed anisocytosis and hypochromia, and there is no reason to doubt that iron deficiency was the cause. Nearly all the patients were admitted because of acute respiratory infection, and, although this was a selected population in that the children were ill, it serves to emphasize the increased morbidity rate that occurs in iron-deficiency anaemia.

Since Helen Mackay demonstrated, over 30 years ago, that nutritional anaemia of infants was a preventable condition there has been little official action, although the general standard of nutrition has improved tremendously in other respects. A recent investigation by the Chicago Board of Health¹ has confirmed that a high incidence of iron deficiency in infants can be reduced by the addition of a small amount of iron to milk. 603 infants were fed from birth until they were 9 months old with a special milk preparation containing 12 mg. of elemental iron per quart (0.95 litre; a British quart is 1.13 litres). They were compared with a control group of 445 infants who were fed on evaporated milk without additional iron. Both groups received vitamin supplements. From the age of 26 weeks there was a significant difference in the mean haemoglobin concentration between the two groups. In the control group 337 (76%) became anaemic (Hb less than 10 g./100 ml.), 299 by the age of 1 year. In the study group 55 (9%) became anaemic, but in more than half of these it did not develop until six months to one year

after the iron supplement had been stopped. The morbidity from infection (especially respiratory infection) differed markedly in the two groups. Nearly 40% of the control group had a respiratory infection between 37 and 52 weeks of age compared with slightly less than 20% in the study group.

These results may not be generally applicable to conditions in this country, as the study was conducted in a poor quarter of Chicago, over 90% of the infants were non-white, and the illegitimacy rate was 30%. They do emphasize, however, that iron deficiency is an important factor in morbidity and that it can largely be prevented by the addition of a small amount of iron to milk. Although the majority of babies probably have sufficient iron at birth to satisfy their needs until they are weaned on to iron-containing foods, the minority who are not so satisfied is substantial enough to justify the addition of iron to all preparations of milk used for artificial feeding.—I am, etc.,

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Liverpool 12.

REFERENCE

- ¹ Andelman, S. L., Andelman, M. B., Sered, B. R., and Forbes, A., *Improving Infant Health by Feeding an Iron-containing Formula*, 1964. Chicago Board of Health, Chicago, Illinois.

Chromosome Studies in Agammaglobulinaemic Subjects

SIR,—The concept that both "typical" and "atypical" agammaglobulinaemia are transmitted by a variety of inheritance patterns has been suggested by certain data.¹⁻⁵ Such a hypothesis raises two questions: Do patients with agammaglobulinaemia have a chromosomal abnormality? And, since the inheritance of "typical" agammaglobulinaemia is sex-linked, do apparently female subjects with this disorder lack one of the X-chromosomes?

In an attempt to answer these questions, we studied the karyotypes of seven patients with agammaglobulinaemia, none of whom showed evidence of an underlying disease such as leukaemia or lymphoma. Two were "typical" males in whom agammaglobulinaemia had developed in early infancy. In four subjects, three males and one female, the symptoms of agammaglobulinaemia had appeared during adult life and had persisted for 10 to 15 years. The seventh patient, an adult female, had idiopathic acquired agammaglobulinaemia and a thymoma. In these patients the serum-gamma-globulin levels were less than 150 mg./100 ml. (normal, 1,200–1,450 mg. by the method used in this laboratory). In an additional subject studied, a female, the serum content of each of the immunoglobulins (YG, YA, and Y1M) was approximately 40% of normal, suggesting a Lyon type of mosaicism.⁶

Specimens of peripheral blood were obtained, and leucocyte cultures were prepared by the method of Moorhead *et al.*⁷ for chromosome counting. Each of the eight subjects had a normal count of 46 chromosomes with apparently normal karyotypes. In a similar study of two patients with hypogammaglobulinaemia, Hanichi and Jordan⁸ also reported a normal count of 46 chromosomes; in both cases, however, the twenty-first pair of chromosomes were metacentric