psychiatric disturbance after use of alpha-methyl dopa ("aldomet"). In two recent series^{1 2} depression has occurred as a not uncommon side-effect of this drug. Smirk reported five cases who showed this symptom out of 53 patients treated and Hamilton *et al.* described three out of 69 hypertensives on methyl dopa.

We would like to report a further case where gross psychiatric changes followed the administration of methyl dopa but where the presentation was more like that of schizophrenia.

A woman aged 34 was admitted as an emergency at the 37th week of her third pregnancy suffering from pre-eclamptic toxæmia. Blood-pressure on admission was 160/120; there was marked oedema of hands, feet, face, and abdomen; and her urine contained 300 mg. protein per 100 ml. She complained of headache and visual disturbance. Treatment was instituted with intravenous infusion of 250 ml. 5% dextrose containing 100 mg. chlorpromazine, 100 mg. promethazine, and 100 mg. pethidine. After a second similar infusion her blood-pressure fell to 140/100 and she no longer complained of headache or blurred vision. She was put on methyl dopa 250 mg. t.d.s., and the dosage raised to 500 mg. t.d.s. over a period of three days, and she was thus maintained. After five days she had a normal delivery of a live male infant. Forty-eight hours later, while she was still having methyl dopa and had been given a total of 7 g. of the drug, she developed psychotic symptoms.

She was dull and retarded and showed marked flattening of affect, presenting the picture of apathetic inertia. She experienced visual, olfactory and tactile hallucinations, and expressed ideas of reference. A diagnosis of toxic psychosis was made and treatment established with intravenous "parentroline." She made an excellent recovery and was discharged on the tenth day of the puerperium.

The toxic psychoses may present widely varying clinical pictures, it being generally accepted that the character of such an illness is to some extent dictated by the pre-morbid personality of the patient. It seems to us possible that the preponderance of depressions reported following methyl dopa may be due to the fact that most of the patients treated with this substance were "hypertensives" and might therefore be expected to possess close similarities of personality. A series of patients suffering from hypertension in pregnancy and treated with methyl dopa might well show up a greater variety of psychiatric syndromes than has already been described.

We would like to thank Mr. D. R. Beaton for permission to publish this case.

—We are, etc.,

Herrison Hospital,
Dorchester, Dorset.

A. G. FULLERTON.

Portway Hospital,
Weymouth Dorset.

D. MORTON-JENKINS.

REFERENCES

¹ Smirk, H., *Brit. med. J.*, 1963, 1, 146.

² Hamilton, M., and Kopelman, H., *ibid.*, 1963, 1, 151.

Side-effects of Monoamine Oxidase Inhibitors

SIR.—We are studying the incidence and mechanism of undesirable reactions when patients who are being treated with monoamine oxidase inhibitors receive pethidine or opium derivatives. So far as we can trace, only about 12 cases have been reported, whereas we have observed three of these ourselves in this hospital, and suspect that the incidence may be widespread.

We are anxious to discover (1) whether this is a common and invariably alarming complication, or (2) whether it depends upon a rare idiosyncrasy. In view of the wide use of monoamine oxidase inhibitors

it seems important to clarify this issue. We should therefore be grateful if this could be brought to the notice of your readers, and we should be obliged if we could have clinical details of any reactions observed, and also a note of any patients who have been known to have received such a combination without ill effects.

—We are, etc.,

St. Thomas's Hospital,
London S.E.1.

J. J. BRADLEY.

J. G. FRANCIS.

"Caprin"

SIR,—I wonder whether I might inquire through your correspondence columns about the experiences of others who may have used a relatively new formulation of aspirin called "caprin"? This product is claimed by West Pharmaceutical Company Limited, the manufacturer, to be free of gastric irritant properties and is advertised as being "... the answer to painful gastric irritation and occult blood loss in long term, high dosage aspirin therapy."

These surprising claims are unsupported by evidence from clinical trials in man. Indeed, in recent correspondence with me the medical department of the company has maintained that "clinical trials in the case of caprin are not necessary, because the therapeutic action of the drug is not in question." Furthermore, no investigation of intestinal blood loss has been carried out by them because "our claim is limited to the effect of caprin on the gastric mucosa."

In circumstances like these one may well question the reliability of the product concerned, and it would be most interesting to know whether anyone else has come to a similar conclusion after using it. Certainly in my limited experience caprin has proved just as capable of producing epigastric discomfort as are "ordinary" aspirin tablets.—I am, etc.,

Lancaster.

B. W. MCGUINNESS.

Antibiotic Growth Stimulation

SIR,—At this Institute we have been studying the mechanism of antibiotic growth stimulation for several years and feel that your annotation on antibiotics as human food supplements (December 15, 1962, p. 1594) calls for some comment. You list three serious objections to the participation of bacteria in antibiotic growth stimulation: (1) The small amount of antibiotic required to produce the effect; (2) the effective antibiotics have radically different structure, antibacterial spectra, and pharmacological properties; and (3) the response of germ-free animals to feeding with antibiotics.

We have reported¹ that low concentrations of penicillin included in the diet of chicks and resulting in a growth response usually eliminate *Clostridium welchii* from their caeca. When *Cl. welchii* was not eliminated its toxigenicity was impaired. The fact that differing antibiotics such as penicillin, aureomycin, streptomycin, oleandomycin, etc., all stimulate growth has been quoted by an eminent authority² as evidence for the participation of bacteria in this phenomenon, since the only factor the antibiotics have in common is an antibacterial one.

The crux of the matter lies in the response of germ-free animals to antibiotics. Luckey, whom you quote,³ is the only worker who has reported the stimulation of growth of the germ-free animal by antibiotics; he used an even lower level than other workers. These experiments have been severely criticized by Jukes,⁴

among others, on the score of the small number of birds used and the great variability among them. Forbes and Park⁵ in excellently controlled experiments found that germ-free chicks grew better than conventional controls and showed no response to penicillin. Forbes and co-workers⁶ obtained similar results when they gave oleandomycin to germ-free turkeys. The Lobund workers also obtained no response on feeding penicillin to germ-free chicks. Recently⁷ we have confirmed that germ-free chicks grow better than conventional birds and show no response to penicillin. We have also found⁸ that *Cl. welchii* inoculated into germ-free chicks depressed growth and that this depression was relieved by the inclusion of penicillin in the diet. Penicillin also caused a "stimulation" of growth when *Cl. welchii* together with other intestinal organisms was inoculated into germ-free chicks.

These results confirm the bacterial theory of antibiotic growth stimulation, and it is our view that certain bacteria normally present in the gut of animals depress the growth rate of the host. This depression can be relieved by the inclusion of antibiotics in the diet. *Cl. welchii* is an example of such an organism; others may yet be discovered.—I am, etc.,

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Shinfield, Berks.

M. LEV.

REFERENCES

- ¹ Lev, M., Briggs, C. A. E., and Coates, M. E., *Brit. J. Nutr.*, 1957, **11**, 364.
- ² Jukes, T. H., *Antibiotics in Nutrition*, 1955, p. 19. Medical Encyclopedia Inc., New York.
- ³ Luckey, T. D., *Antibiotics, Their Chemistry and Non-medical Uses*, 1959, edited by H. S. Goldberg and D. van Nostrand. Princeton, New Jersey.
- ⁴ Jukes, T. H., *Antibiotics in Nutrition*, 1955, p. 28.
- ⁵ Forbes, M., and Park, J. T., *J. Nutr.*, 1959, **67**, 69.
- ⁶ ———, Supplee, W. C., and Combs, G. F., *Proc. Soc. exp. Biol. (N.Y.)*, 1958, **99**, 110.
- ⁷ Coates, M. E., Fuller, R., Harrison, G. F., Lev, M., and Suffolk, S. F., *Brit. J. Nutr.*, 1963, **17**, 141.
- ⁸ Lev, M., and Forbes, M., *ibid.*, 1959, **13**, 78.

Hazards of Drugs in Pregnancy

SIR,—In your leading article entitled "More Hazards of Drugs in Pregnancy" (January 19, p. 138) you discuss the report of Werboff and Kesner.¹ I am writing to give you a critical consideration of this paper for which you so appropriately call.

Werboff and Kesner gave meprobamate to pregnant rats during certain periods of gestation and reported that the drug may have detrimentally altered the maze learning ability of the offspring. The ability of rats to run the maze in 20 seconds or less in two out of three errorless trials was taken as the criterion of learning. It is well known that maze performance in animals is affected not only by the ability of the animals to learn but also by their physical condition. The authors, however, used animals that weighed less and were significantly less active on two separate activity measures.² This observation requires two comments. Firstly, animals showing motor impairment are not suitable for evaluation in a maze because their performance will be indicative of their motor disability rather than of their ability to learn. This consideration is particularly pertinent when the time to complete a run is taken as the criterion of learning as has been done by these authors. Secondly, it is known that offspring of rats given meprobamate prior to and during the whole period of pregnancy in similar or larger doses than given by Werboff and Kesner grow normally and do not weigh less than control animals and are not less active than offspring of untreated animals.³ Thus, it is apparent

that the animals used by Werboff and Kesner must have been diseased and unsuitable for comparison of their maze performance with healthy rats.

It is also of interest to note that Werboff and Kesner administered meprobamate to animals only during one single period of gestation, which was either from day 5 to 8 or from day 11 to 14 or from day 17 to 20. The authors state that it did not make any difference in which trimester of pregnancy the drug was given.² Since the drug is alleged to have an effect on the development of the brain, one would expect that it would have a time-defined influence limited to certain critical stages of the brain's development.

I agree that results of drug studies in animals deserve serious consideration. It is, however, necessary that they be carefully planned, properly executed, and critically evaluated.—I am, etc.,

Wallace Laboratories,
Cranbury, New Jersey, U.S.A.

F. M. BERGER.

REFERENCES

- ¹ Werboff, J., and Kesner, R., *Nature (Lond.)*, 1963, **197**, 106.
- ² ——— and Havlena, J., *Exp. Neurol.*, 1962, **6**, 263.
- ³ Berger, F. M., *J. Pharmacol. exp. Ther.*, 1954, **112**, 413.

"Alka-seltzer" and Haematemesis

SIR,—Your correspondent Dr. A. C. Arthur does well to draw attention to the dangers of "alka-seltzer" in causing gastro-intestinal bleeding (January 26, p. 260). Possibly some doctors, and certainly most laymen, do not realize that another proprietary preparation—namely, "Beecham's powder"—contains 5 gr. (0.32 g.) of aspirin in each powder. They are "recommended" for colds, influenza, headaches, various forms of "rheumatism," etc., in doses of one powder every two or three hours "as necessary." This can obviously result in taking 60 gr. (4 g.) of aspirin unknowingly in 24 hours, with possibly disastrous results in patients sensitive to aspirin. Such products should be clearly labelled "Contains Aspirin."—I am, etc.,

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Church Village, Glamorgan.

J. DE SWIET.

High-dose Mustine Therapy

SIR,—Dr. K. P. Goldman (February 2, p. 312) gave a "maximal sublethal dose" of mustine (0.8 to 1.0 mg./kg. body weight) in three divided doses on consecutive days to 32 patients with advanced bronchial carcinoma. There was a subjective improvement in 56% and an objective response in 43%, the average remission time being a few weeks only. Twenty-seven of the 32 patients died within six months.

After pointing out that "there is little reason to believe that mustine therapy appreciably prolongs life except in cases of superior mediastinal compression," Dr. Goldman admits that the drug given in these doses might well hasten death (in 16% of cases in this series).

Few practitioners can quarrel with Dr. Goldman's observation that "satisfactory results in lung cancer chemotherapy will probably have to await the discovery of new drugs which are less damaging to normally dividing tissues." His final conclusion that in the meantime "the best palliation can be achieved with the drugs at present available if they are given in maximal doses" rather suggests, however, that he has failed to accept the message provided so beautifully by his own clinical trial.

When used in the treatment of advanced disseminated solid tumours the anti-cancer drugs are, at best, pallia-