epidemiological grounds the case against the food-borne hypothesis is still open.—I am, etc.,

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Adjuvants to L-dopa for Parkinsonism

SIR,—Notwithstanding the generally satisfactory response of Parkinsonian patients to L-dopa, undesirable side-effects and the high cost of the drug have led to attempts to reduce dosage with the aid of other agents. Success in this field has been reported using dopa-decarboxylase inhibitors,¹ which, since they do not pass the blood brain barrier, act so as to prevent peripheral "wastage" of dopa. However, these preparations have not yet become generally available, and it was thought that mention of two other attempts to enhance the effectiveness of relatively small doses of L-dopa, albeit unsuccessful, might be of practical and theoretical interest.

The following schema shows some of the pathways by which dopa is converted to its various end products; the enzymes involved are bracketed. Dopa — (dopa-decarboxylase) — dopamine.

Pathway 1. — Dopamine — (dopamine beta-oxidase) — noradrenaline.

Pathway 2. — Dopamine — (monoamine oxidase) — dopac — (catechol-*o*-methyltransferase) — homovanillic acid.

Pathway 3. — Dopamine — catechol-*o*-methyltransferase) — methoxytyramine — (monoamine oxidase) — homovanillic acid.

Since pyridoxine is a co-factor in the enzymatic activity of dopa decarboxylase, alterations in concentration of this vitamin might be expected to influence conversion of dopa to dopamine. The administration of pyridoxine has been reported to have reduced the anti-Parkinsonian effectiveness of a given dose of L-dopa.² On the assumption that this was due to enhanced extracerebral (and hence therapeutically undesirable) conversion of L-dopa to dopamine it was decided to combine L-dopa therapy with the anti-tuberculosis drug isoniazid, which causes marked depletion of body stores of pyridoxine.

Five Parkinsonian patients were maintained on 1-2 g. L-dopa for a week and their status recorded with regard to akinesia, rigidity, and tremor. Isoniazid (5 mg./kg.) daily was added, and the patients observed for a period of 10 days. No change in clinical signs was noted. Another trial involved an attempt to inhibit the enzyme dopamine beta-oxidase (Pathway 1 above) by administration of disulfiram (Antabuse). This has been shown experimentally to increase dopamine levels in the caudate nucleus, hypothalamus, and brain stem with marked reduction of brain stem noradrenaline.³ It has also diminished motor restlessness in cats induced by previous medication with L-dopa, pheniprazine (a monoamine oxidase inhibitor), and reserpine.⁴ Four Parkinsonian patients stabilized as above on 1 g. L-dopa daily were given antabuse 0.5 g. t.i.d. for 9 days together with ascorbic acid (a potentiator of the Antabuse block by virtue of its action as a reducing agent.) Again, no improvement could be related to combined therapy

An explanation for this disappointing result probably lies in evidence that not more than 3% of exogenous dopamine is metabolized to noradrenaline,⁵ so that even if total enzymatic block had been achieved the corresponding increase of dopamine would probably have been only marginal. The hoped-for but unrealized aims of these trials were to obtain greater effectiveness from low doses of L-dopa by adding other agents in quantities known to be therapeutically safe. It is possible that higher dosage levels in experimentally induced extrapyramidal syndromes in animals would throw light on the mode of action of L-dopa, perhaps less simple than has hitherto been believed.

Another theoretical means of increasing dopamine stores would be by blocking the enzyme catechol-*o*-methyltransferase which leads eventually to the formation of homovanillic acid (Pathway 3 above). Pyrogallol is a catechol-*o*-methyltransferase blocking agent, but seems to be too toxic for trial in humans.—I am, etc.,

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REFERENCES

- 1 Tissot, R., *Presse Médicale*, 1969, 77, 617.
- 2 Duvoisin, R., et al. quoted by Cotzias G. C., Papavasiliou, P. S., and Gellene, R. *New England Journal of Medicine*, 1969, 281, 272.
- 3 Goldstein, M., and Nakajima, K. *Journal of Pharmacology and Experimental Therapeutics*, 1967, 157, 96.
- 4 Reis, D. J., Moorhead, D. T., and Merlino, N., *Archives of Neurology*, 1970, 22, 31.
- 5 Rutledge, C. O., and Jonason, J., *Journal of Pharmacology and Experimental Therapeutics*, 1967, 157, 493.

Prophylaxis of Venous Thrombosis

SIR,—In an article on diagnostic accuracy in venous thrombosis (18 April, p. 142) it is claimed that the ¹²⁵I-labelled fibrinogen test is too complicated and time-consuming to be used as a routine procedure for screening high risk patients. This is true of the technique used by the authors. However, it has now been superseded in most centres in Britain by the ratemeter.¹ The test is performed by a technician or physiotherapist and takes only a few minutes. We have now arrived at the situation where we could argue with equal force that a haemoglobin estimation is too complicated and time-consuming. The article adds no new information to what has already been published^{2,3} and confirmed by others.⁴

In the second article by the same authors on dextran-70 in the prophylaxis of post-operative venous thrombosis (18 April, p. 144) it was disappointing to see the unequivocal support which they have given to the idea that dextran-70 is an efficient method of prophylaxis in preventing post-operative venous thrombosis. In a recent symposium⁵ devoted entirely to this subject the evidence from many centres regarding the usefulness of dextran-70 was conflicting. We have been unable to show any significant reduction in the incidence of deep vein thrombosis in a group of 58 surgical patients who received dextran-70, when compared with a control group receiving no prophylactic measures.⁵ In addition, the dangers of this therapy in high risk patients, very often elderly patients undergoing major operations, must be emphasized. In our series, two patients de-

veloped alarming symptoms and dextran-70 had to be discontinued. One patient developed acute massive pulmonary oedema and died, and the other developed acute heart failure from which he recovered.

In the absence of really effective prophylaxis, treatment is still an important feature. It is much more effective when carried out at the earliest possible moment in those patients where thrombi are spreading from the calf into the larger veins. It is in this group that there is a real danger of pulmonary embolism.⁶ To accomplish this at the present moment the best method is to screen all patients "at risk" with the ratemeter, and to institute treatment at the proper time.—We are, etc.,

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REFERENCES

- 1 Kakkar, V. V., Nicolaides, A. N., Renney, J. T. G., Friend, J. R., and Clarke, M. B., *Lancet*, 1970, 1, 540.
- 2 Flanc, C., Kakkar, V. V., and Clarke, M. B., *British Journal of Surgery*, 1968, 55, 742.
- 3 Kakkar, V. V., *Annals of the Royal College of Surgeons of England*, 1969, 45, 257.
- 4 Nezus, D., Pinto, D. J., Le Quesne, L. P., Brown, N., and Chapman, M., *British Journal of Surgery*, 1968, 55, 835.
- 5 Symposium on Use of Dextran-70 (Macrodex) in Prevention of Deep Vein Thrombosis. February, 1970.
- 6 Renney, J. T. G., Kakkar, V. V. and Nicolaides, A. N. Paper delivered to the Surgical Research Society of Great Britain and Ireland, meeting January 1970.
- 7 Kakkar, V. V., Howe, C. T., Flanc, C., and Clarke, M. B., *Lancet*, 1969, 2, 230.

Use of Broad-spectrum Antibiotics

SIR,—I have recently received a number of wall charts entitled *The Beecham Range of Penicillins*, for display in our hospital wards, presumably as a guide to treatment for the junior medical staff. Under the column entitled "Indications" there are several entries with which many bacteriologists would not agree, but one of the entries under Ampiclox Neonatal (ampicillin and cloxacillin) prompts me to write to you.

This broad spectrum combination is advocated for "Treatment of confirmed or suspected infections in neonates including Pneumonia, Septicaemia, 'Failure to thrive'" (my italics). It is the recommendation for the empirical use of such a powerful combination of drugs which I find particularly disturbing. Antibiotics are already used uncritically enough in man. The Swann report¹ endorsed the disquiet previously expressed about the disastrous results of their indiscriminate use in calves, with the consequent selection of enteric pathogens with multiple drug resistance. There is no reason for supposing that human infants are immune to similar effects.

Apart from this probable long-term influence of the indiscriminate use of these valuable drugs there is, I think, another real danger in adopting such recommendations. Administration of broad-spectrum antibiotics results in a profound alteration in the normal flora of the body and renders the patients especially susceptible to colonization by multiply resistant organisms, particularly *Pseudomonas* sp., *Staph. aureus*, and *Candida* sp., and many bacteriologists believe that patients on such drugs should be nursed in isolation. This is seldom possible,

but I believe that any infant who has been given Ampiclox by his general practitioner and who subsequently has to be admitted to a paediatric ward, with its high environmental content of resistant organisms, is in real danger of acquiring such organisms with perhaps serious or even fatal consequences.—I am, etc.,

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REFERENCE

- ¹ Ministry of Agriculture, Fisheries and Food and the Secretary of State for Wales. *Antibiotics in Animal Husbandry and Veterinary Medicine*, London, H.M.S.O., 1969.

Phage Treatment of Severe Burns

SIR,—Dr. G. Shera's recording of the clearing up of septic lesions by gauze dressings soaked in broth culture filtrates of the causative organism (28 February, p. 568) recalls experiences of some years ago when I was working in the clinical laboratory of the Manchester Royal Infirmary.

Fleming had recently published his paper describing the antibacterial action of his famous mould. I obtained a culture from him and we tried out gauze dressings soaked in broth culture filtrates for septic lesions. The yield of penicillin as judged from the colour of the filtrates was inconsistent, as were the clinical results. But we noticed that even filtrates lacking the characteristic golden colour sometimes seemed to have a beneficial effect, so we tried gauze swabs soaked in sterile broth and gained the impression that they often helped to clean up the lesion. I just wonder whether Dr. Shera's results were due to a non-specific effect of the broth rather than to phage, as he does not present any evidence in his letter that phage was present in the filtrates.—I am, etc.,

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Evaluation of Simpson

SIR,—I enjoyed reading Mr. E. Gaskell's account of "Three Letters by Sir James Young Simpson" (16 May, p. 414). Not only was it full of new information but in addition, what was perhaps not intended, it showed a hollow sham. We all know of course that Simpson discovered anaesthesia; or if we don't it is not for want of his telling us. That he did not discover anaesthesia might be compensated for by his discovery of chloroform; yet even this was presented to him by Waldie, and Simpson passed it on to the world with quite the minimum of care and experiment. Fortunately for his reputation chloroform is such a perfect anaesthetic that its dangers were small in

relation to the risks of pre-antiseptic surgery and midwifery.

His pathetic notes described by Mr. Gaskell, dashed off casually on his pathetic pamphlets (pathetic in each case set against what most scientific writers would put in similar circumstances), are clearly designed for the one purpose of placing his views and enthusiasms before as many friends and colleagues as possible. He had nothing to learn from modern publicists and, as I see it, his enormous reputation was and is built up on no valid basis.

Compare his presentation of chloroform with that of William Withering's of digitalis, an equally potent and useful drug. Ten years of trial and discussion went to the latter, and the thesis contained an unselected series of 163 cases. Compare with Lister, who continued to do scientific experiments for years both before and after his original publication to make his argument sound. Compare even with Simpson's pupil and alleged natural son Lawson Tait, who devised and perfected such a variety of novel operations, and one cannot but be struck by the paucity of Simpson's scientific achievement—not as Mr. Gaskell would have it "extraordinary to the point of brilliance"; if anything this could only describe his self advertisement.

Apart from chloroform, what have we? There is the uterine sound—no more than an improvement of an instrument used in classical antiquity; there was acupuncture—another old idea that never caught on despite his enthusiasm; there was the air tractor, which despite his claim to have hit on the idea many years before, appeared suspiciously close to that of Dr. Neil Arnott.

It is undoubtedly true that he was an exceptional man. All his contemporaries are unanimous about this. He was a very great teacher and should be honoured in Edinburgh for this. His part in the development of anaesthesia deserves to be remembered by anaesthetists. He was a good antiquarian, far in advance of his time, and should be honoured by archaeologists.

Despite all this it is just not true to say he was one of the great pathfinders of medicine. One hopes that when the inevitable celebrations of the centenary of his death have passed we may then allow him to revert to his proper and important but still subordinate place in medical history.—I am, etc.,

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Pregnancy and Crohn's Disease

SIR,—We agree with Mr. A. H. Imrie (2 May, p. 299) that Crohn's disease can on occasion be a serious complication of pregnancy. A survey by one of us described a maternal death from this cause.¹ Recently we have encountered a similar patient, who recovered after operative treatment but only after suffering several days of critical illness.

A woman, aged 26 years, underwent laparotomy on 28 April 1967 for suspected appendicitis. Subacute Crohn's disease

affecting the terminal ileum was found, so the appendix was not removed. There were no post-operative complications, and a barium enema showed changes in the terminal ileum confirming Crohn's disease. At follow-up visits afterwards her condition remained satisfactory. Five months later she became pregnant for the third time, and as her two previous confinements had been normal her family doctor acceded to her request for a home confinement. She remained well for most of the pregnancy, but from 36 weeks onwards complained of increasingly severe abdominal pains so that on several occasions her midwife thought that labour was imminent.

She had a spontaneous delivery at term of a healthy infant weighing 8lb. 6oz. (3,796 g.). The patient experienced severe abdominal pain during labour which eased for the 1st day of the puerperium but then recurred. By the fifth day of the puerperium she was obviously very ill, with severe pain, and was admitted to hospital. On examination there was evidence of widespread peritonitis, and after reference to her old case notes a diagnosis of acute Crohn's disease was made. After a few hours' resuscitation and rehydration operation was performed on 25 June 1968. The terminal ileum and ascending colon were grossly inflamed, and there were several pockets of pus in the peritoneal cavity. The ileum was transected above the diseased portion and end-to-side ileo-transverse colostomy performed. After a stormy convalescence, complicated by a chest infection, she eventually recovered and was discharged home four weeks later. Her subsequent progress was satisfactory but she remains under medical supervision with slight frequency of bowel action.

Drs. J. F. Fielding and W. T. Cooke (11 April, p. 76) were fortunate not to have encountered any such serious complications among their excellent results reported from Birmingham. However, a careful review of the literature confirms our view that when major complications do occur there is a very real threat to the life of mother and fetus.²⁻⁴

The differential diagnosis of abdominal pain in pregnancy and labour is notoriously difficult, and for obvious reasons radiographic investigation of the gastrointestinal tract is contraindicated. If the case just described had been referred to us early in pregnancy we would have considered termination justifiable, although we agree with Drs. Fielding and Cooke that with careful supervision the majority of such patients will avoid serious complications. However, in a few cases the risks may be considerable and should not be ignored. We feel that support is lent to our view by the interesting letters on this subject from Dr. B. Heyworth and others and Dr. P. F. Schofield and others (9 May, p. 363).—We are, etc.,

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REFERENCES

- Jones, R. L., and Soltau, D. H. K., *Journal of Obstetrics and Gynaecology of the British Empire*, 1958, **65**, 811.
- Babson, W. W., *New England Journal of Medicine*, 1946, **235**, 544.
- Blair, J. S. G., and Allen, N., *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1962, **69**, 648.
- Williams, D. L., and Davis, D. R., *Southern Surgeon*, 1946, **12**, 342.