then be easily passed through after lifting the staples in one corner.

The observation room is completely blacked out and the room under observation brightly illuminated. The observers should preferably wear dark clothes or a dark smock as white or pale colours will reflect the light coming through from the interview room. The screen is not, of course, sound-proof; while this means the observers must keep still, it obviates the need for microphones, amplifiers, etc.

A notice board can be fitted over (on either or both sides) when the screen is not in use. If the board is fairly thick or padded the rooms will be as sound proof as they ever were.—I am, etc.,

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Unbalanced Deoxyribonucleotide Synthesis Caused by Methotrexate

SIR,—The report by Dr. A. V. Hoffbrand and Miss Edith Tripp (15 April, p. 140) of changes in the pools of deoxynucleoside triphosphate in cells exposed to methotrexate is of great interest. Their results are, however, different from those recently reported by Baumunk and Friedman,¹ who found that the deoxythymidine triphosphate (dTTP) content of HeLa cells was not altered by exposure to methotrexate or 5-fluorouracil. Their statement that a rise in deoxyadenosine triphosphate (dATP) levels inhibits ribonucleotide reductase, although certainly true for some bacterial and mammalian systems, is not true for all mammalian cells.² Furthermore, the ribonucleotide reductase activity of bone marrow cells from patients with pernicious anaemia has been found to be greatly increased,³ and this would appear to conflict with Dr. Hoffbrand and Miss Tripp's suggestion that ribonucleotide reduction may be inhibited in megaloblastic cells. Lastly, their suggestion that DNA ligase activity may be inhibited in methotrexate treated cells is a most interesting and easily testable hypothesis. However, Cleaver⁴ has studied DNA repair in HeLa cells exposed to a wide variety of cytotoxic agents. He was unable to demonstrate any defect in DNA repair in cells exposed to cytosine arabinoside or fluoro-deoxyuridine, both agents which induce megaloblastic change.

I have measured the pools of purine and pyrimidine deoxynucleoside triphosphates in mouse L5178Y lymphoma cells following their exposure to methotrexate.⁵ In every experiment the level of dTTP in treated cells has been reduced, but no consistent change in dATP has been found. It may be that the discrepancy between my results and those of Dr. Hoffbrand and Miss Tripp is explained by the different cell lines studied and by the fact that my cells are a heterogeneous population while the latter's cells are synchronized by their exposure to phytohaemagglutinin.

Finally, a mechanism for the well-recognized masking of megaloblastosis by iron deficiency⁶ does emerge from Dr. Hoffbrand and Miss Tripp's observation. Iron is a cofactor for mammalian ribonucleotide reduction⁷ and in its absence reduction of ADP→dADP will be inhibited, thus pre-

venting a rise in the dATP level, which they maintain is the basis for megaloblastic change.—I am, etc.,

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- 1 Baumunk, C. N., and Friedman, D. L., *Cancer Research*, 1971, 31, 1930.
- 2 Fujioka, S., *Acta Haematologica*, 1971, 45, 136.
- 3 Fujioka, S., and Silber, R., *Journal of Laboratory and Clinical Medicine*, 1971, 77, 59.
- 4 Cleaver, J. E., *Radiation Research*, 1969, 37, 334.
- 5 Tattersall, M. H. N., Furness, M. E., Jackson, S., and Harrap, K. R., *Proceedings of the Biochemical Society*, in press.
- 6 Van der Weyden, M., Rother, M., and Firkin, B., *British Journal of Haematology*, 1972, 22, 299.

Removal of Extruded I.U.D.

SIR,—Six days after reading Dr. Ursula E. Mountrose and Mr. W. L. Whitehouse's letter (8 April, p. 113) recommending colpotomy to remove an I.U.D. extruded into the pouch of Douglas a 23-year-old patient was referred complete with x-ray (Fig.). The Lippes loop had been inserted on 6 April 1972, six weeks after confinement, with no difficulty or symptoms at that time, but the threads could not be seen or felt five days later. The only subsequent complaint had been vague pelvic discomfort.

The uterus was anteverted and well involuted, and on careful bimanual examination the loop could be felt in the hollow of the sacrum. She was admitted with her breast-fed baby two days later for colpotomy under anaesthesia. One finger through into the pouch of Douglas easily located and removed the loop. There was no reaction and she went home 48 hours later. I would agree with Dr. Mountrose and Mr. Whitehouse that colpotomy should be considered whenever the extruded loop remains in the pelvis.—I am, etc.,

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Bran and Diverticular Disease

SIR,—As Mr. Neil S. Painter and others (15 April, p. 137) refer to my own experience, it may be constructive to say that I used unprocessed bran in the Royal Navy for some 30 years. At first I experimented cautiously on myself, but my first communication (22 March, 1941, p. 461) described 10 years of constantly-widening experience with this material. I was at that time the senior medical officer of the battleship *King George V* and, owing to the scarcity of fresh

fruit and vegetables, found such bran invaluable for correcting the constipation afflicting the ship's company. The ship's canteen bought the bran by the hundred-weight-sack and sold it at the present equivalent of only 1p per lb—which amount often lasted a man for several weeks. The sailors loved the stuff by comparison with purgatives, and on one occasion, when the supply failed, many fell in at "Captain's Request-Men" to ask if it could be restored, as they felt its loss greatly. I think it is a great tragedy of our present age that, with M.R.C. workers^{1,2} showing at least 15% of the population to be on regular purgatives, this precious material is ever lost through the manufacture of white flour.

I have not only used unprocessed bran with almost invariable success among thousands of naval personnel at sea, as described above, but also for nearly 20 years during specialist duties as a physician in naval hospitals, where I always declined to prescribe aperients, relying on an enema if any serious arrest was already present and then solely on the unprocessed bran for future prevention. I can understand that old or frail people would require gradual habituation to it but this was never a problem in the Navy, as long as the bran was taken *before* meals, to prevent any overloading of the stomach. Meanwhile, the cheapness and naturalness of this product not only facilitate its use on an institutional scale, but also correct certain vitamin deficiencies that can be very real in old people, especially if living alone.

I must disagree entirely over one crucial point in Mr. Painter and colleagues' article. The introduction of the roller mills in 1880 made precious little difference to the amount of fibre removed from the flour. The reason for this is that the fibre (bran) is placed by nature on the outside of the grain, to protect it from injury. Therefore it is the first substance to be removed in the milling. Indeed, Horder, Dodds, and Moran³ have shown clearly that even a 90% flour (that is one that contains 90% of the whole grain) has already lost two-thirds of the fibre present, and the extra loss of fibre that arose when the old stone-milled 80% flour, introduced over a century earlier, was replaced by the roller-milled 70% flour around 1880 amounted to only about 1%.

No. As I have argued,^{4,5} the various diseases that sprang into prominence in the latter part of the nineteenth century, in which I included the intestinal conditions of appendicitis and diverticular disease, owed much to the refining of flour, but still more to the refining of sugar, the consumption of which, as shown in my chart in Mr. Painter's article, was rising at that time with frightening speed. Not only is much more fibre lost in the refining of sugar, but the effect of the sugar on the proliferation of the *E. coli* and other bacterial inhabitants of the intestines is of decisive importance.

None of this, however, in any way alters the importance of a true wholemeal bread in our nutrition today, and far from reducing its bran content to any extent whatsoever, it is far more logical to add an extra 10% of bran, so as to effect at least some compensation for the fibre lost in the refining of sugar. This extra bran adds to, rather than detracts from, the flavour, and such bread is now being increasingly produced in London as the "bran plus" loaf which I have described in our joint work. Such bread is obviously of particular indica-