

designed to make exceptions but to explain how the standstill should be operated in circumstances where existing pay is directly related to output or turnover, or, for workers with fixed hours, to the amount of overtime worked. Hospital junior doctors' salaries do not fluctuate from day to day with variations in output, turnover, or number of hours, and therefore it seems the paragraph does not apply to them.

However ambiguous the paragraph in the White Paper may be, neither its terms nor the Minister's interpretation of them are negotiable. The Government intends that there should be no exceptions to the pay-freeze. The B.M.A. itself has already stated that any exceptions in favour of other sections of the community to the exclusion of doctors would be an immediate resignation issue. It is not difficult to imagine the reaction of others to any exception in the case of the doctors. But this does not lessen the sympathy that all—including the public—will have for the young doctors in a harsh situation that has been forced upon them, nor the grave anxiety about its effects on the future of the hospital service. The Minister of Health's proposals for alleviating the grosser hardships that the freeze will cause some junior medical staff are what any good employer would make, and they will be seen as such. A genuine welcome, however, may be given to the Government's agreement that a doctor who moves down to a lower grade for training should not lose pay or seniority. In the same spirit the Government could well reimburse, during the pay-freeze, certain professional expenses incurred by junior doctors—for example, fees for registration and membership of a defence society, and examination fees and subscriptions to libraries and learned societies, which are part of the heavy cost of higher training.

Test of Pituitary-Adrenal Function

Lysine vasopressin has recently attracted interest because it causes a prompt rise in the level of cortisol in the plasma. This action is mediated by release of corticotrophin from the anterior pituitary gland. Consequently the response to lysine vasopressin can be used as a test of pituitary-adrenal function.

Lysine vasopressin is an octapeptide similar in structure to oxytocin. It is found only in the posterior pituitary gland of the hog,¹ hippopotamus, and peccary (a pig-like beast of Central and South America).² It differs from arginine vasopressin, the human antidiuretic hormone, in its greater stability and by the substitution of lysine for arginine at position 8 of the peptide chain. Since its synthesis was achieved³ its main use has been in the treatment of diabetes insipidus, when nasal sprays are sometimes very effective.⁴

Although vasopressin causes release of corticotrophin in man,⁵ there is good evidence that it does not play a major part in the normal regulation of the release of this hormone.⁶⁻⁷ Regulation is normally mediated by polypeptides produced in the hypothalamus, and they reach the anterior pituitary by way of the local portal circulation. These corticotrophin-releasing factors are of two types— α and β . The β factor closely resembles vasopressin and is the more active.

The mechanism by which lysine vasopressin causes a rise in plasma cortisol in man is not yet fully understood. It could act on the hypothalamus or higher centres, on the anterior pituitary, or on the adrenal cortex. There seems little doubt that it does not stimulate the adrenal directly in

man, since its effect can be blocked by morphine and dexamethasone,⁵ neither of which affect the adrenal response to corticotrophin. Experiments in rats have shown that hypophysectomy abolishes the effect of vasopressin,⁸ but this finding requires confirmation in man. The claims by J. Landon and colleagues⁹ and G. Gwinup⁵ that lysine vasopressin acts directly on the pituitary in man warrant further investigation, since if this hypothesis is correct it could be used to distinguish between pituitary and hypothalamic lesions, a distinction which cannot be made with available tests.

The present tests of pituitary-adrenal function employ stimulation of the adrenal by exogenous corticotrophin, or by endogenous corticotrophin released in response to a metyrapone-induced fall in plasma cortisol or to the stress of insulin-produced hypoglycaemia or to pyrogen injections. High doses of synthetic steroids such as dexamethasone can also be used to inhibit the adrenal by reducing release of pituitary corticotrophin. Tests that use corticotrophin as a stimulant evaluate only adrenocortical function, while the corticotrophin-mediated adrenal response to stress or to alterations in the levels of circulating corticosteroid cannot be used to separate pituitary from hypothalamic lesions, because they assess the integrity of the whole hypothalamic-pituitary-adrenal axis. This complex situation has been well summarized by C. L. Cope,¹⁰ who concludes that "the corticotrophin release mechanism does not consist of a single centre responding to stimulant, inhibitory or stressful stimuli but that a much more complex mechanism is involved in which each of these forms of influence is capable of exerting its own effect independently of the others and probably through a separate chain of events."

Landon and colleagues⁹ have compared the lysine vasopressin test with other tests of pituitary-adrenal function in patients with pituitary or hypothalamic disorders and in normal controls. Patients with pituitary tumours responded in three ways. In some of them all tests were normal, showing the integrity of the whole system. In others all tests were abnormal, since disturbance of function was enough to cause adrenal atrophy. A third group of patients had a normal response to lysine vasopressin and corticotrophin but not to metyrapone or insulin. These patients had x-ray evidence of suprasellar extensions of the tumour and responded to the tests in the same manner as patients with presumed hypothalamic lesions. This clinical evidence appears to support the view that a normal response to the lysine vasopressin test combined with abnormal responses to insulin or metyrapone indicates a lesion in the hypothalamus rather than the pituitary. An alternative possibility is that lysine vasopressin acts on hypothalamic centres separate from those involved in the other tests.

Methods of carrying out the lysine vasopressin test vary but all entail estimation of a baseline level of plasma cortisol

¹ Popenoe, E. A., Lawler, H. C., and Du Vigneaud, V., 1952, *J. Amer. chem. Soc.*, **74**, 3713.

² Heller, H., *Symp. Zool. Soc. Lond.* No. 9, p. 93, 1963.

³ Bartlett, M. F., Jöhl, A., Roeske, R., Stedman, R. J., Stewart, F. H. C., Ward, D. N., and Du Vigneaud, V., *J. Amer. chem. Soc.*, 1956, **78**, 2905.

⁴ Bartrop, D., *Lancet*, 1963, **2**, 276.

⁵ Gwinup, G., *Metabolism*, 1965, **14**, 1282.

⁶ Leeman, S. E., Glenister, D. W., and Yates, F. E., *Endocrinology*, 1962, **70**, 249.

⁷ Shuster, S., *J. Endocr.*, 1960, **21**, 171.

⁸ Vernikos-Danellis, J., *Endocrinology*, 1964, **75**, 514.

⁹ Landon, J., James, V. H. T., and Stoker, D. J., *Lancet*, 1965, **2**, 1156.

¹⁰ Cope, C. L., *Adrenal Steroids and Disease*, p. 297. London, 1965.

¹¹ Mattingly, D., *J. clin. Path.*, 1962, **15**, 374.

¹² Ribot, S., Green, H., Small, M. J., and Abramowitz, S., *Amer. J. med. Sci.*, 1961, **242**, 612.

by the Mattingly¹¹ technique, followed by administration of lysine vasopressin by intramuscular injection⁵ or intravenous infusion⁹ and serial estimations of the plasma cortisol. The maximum value usually occurs after one hour, when control levels exceed 23.6 µg. per 100 ml. of plasma.⁵ Side-effects have been slight, including pallor, increased intestinal mobility, and uterine contractions. It would seem wise to avoid the test in patients with clinical evidence of ischaemic heart disease, since vasopressin may constrict coronary vessels.¹² No changes in blood-pressure have been recorded.⁵

Further studies are required to localize the precise site of action of lysine vasopressin in man. The evidence suggests that it acts by releasing pituitary corticotrophin and not by direct stimulation of the adrenal cortex. Whether it does so or not, it should be useful in the investigation of pituitary and hypothalamic disorders, since it appears to act by mechanisms independent of those operated in existing tests.

Transmission of Disease by Blood Transfusion

Hepatitis,¹ syphilis, malaria, and brucellosis have all been transmitted to patients who were given whole blood or blood products. Hepatitis is by far the most serious disorder transmitted in this way, and the incidence of the disease in patients receiving an average of two bottles of blood is about 0.8%. When plasma from relatively large pools is used the incidence can reach the alarming figure of 11.9%, but if the plasma pool is prepared from less than 10 bottles the figure falls to 1.3%. After a massive blood transfusion—and between 10 and 20 bottles is commonplace in modern heart surgery—the risk is once again increased. This important hazard of blood transfusion is not as widely appreciated as it should be: one of the reasons for this may be the relatively long incubation period, which varies from 60 to 160 days before jaundice appears.

The signs and symptoms are better known. In addition to jaundice, about two thirds of patients have nausea, vomiting, and anorexia, joint pains are present in about a quarter and a skin rash may develop. The illness lasts about 30 days. Seven out of 134 cases reported by D. Lehané and his colleagues² died. The work of G. S. Mirick, R. Ward, and R. W. McCollum³ suggested that giving gamma-globulin may reduce the frequency of hepatitis after transfusion, and there is much to be said for adopting this form of prophylaxis with large transfusions.

Where malaria is endemic the transmission by transfusion remains a hazard. N. N. Duhanina and T. A. Zukova⁴ report 47 cases, including the transmission of quartan malaria to children who were given maternal blood as prophylaxis against measles. Another 36 cases are recorded from Yugoslavia.⁵ Transmission of malaria by transfusion can be prevented by the administration of chloroquine diphosphate to the recipient before the transfusion. A dose of 600 mg. seems to be adequate.⁶

Transmission of syphilis is less likely because spirochaetes are unlikely to survive for more than 72 hours in stored citrated blood,⁷ and transmission of brucellosis, though reported,⁸ must be a rarity.

Most transfusion services do not accept as donors those who give a history of jaundice. Nevertheless, even after this step is taken the known incidence of homologous serum jaundice suggests that not less than 1 in 200 healthy donors are carriers of the virus. Whole blood from donors who have lived in areas where malaria is endemic should not be transfused, though there is no objection to the use of their plasma. It is also the practice to carry out serological tests for syphilis on donor blood samples and to exclude donors giving positive reactions.

Karachi Meeting

At page 107 of this week's *Supplement* is printed the programme of the Joint Annual Meeting of the B.M.A. and the Pakistan Medical Association, to be held in Karachi from 19 November to 3 December. The President-Elect, Professor Hamid Ali Khan, and his committee have produced a varied scientific programme and have drawn speakers from Africa, Asia, and Britain. Certainly no one who has read the programme need seek any further justification for leaving the British winter for the warmth and hospitality of Pakistan. Delegates to the meeting will also have the chance of attending some other medical meetings in Asia and the Far East. The World Medical Association is holding its twentieth General Assembly in Manila from 6 to 12 November, and has arranged the Third World Conference on Medical Education, which will take place in New Delhi from 20 to 25 November. Other congresses taking place in October and November include the Fifth World Conference of Cardiology in New Delhi and the Ninth International Cancer Congress in Tokio.

Registration forms are now available for the Karachi Meeting and may be obtained from the Secretary, Joint Annual Meeting, Karachi, 1966, B.M.A. House, Tavistock Square, London W.C.1. A tour has been arranged in connexion with the Meeting at an inclusive cost of £302 10s. Details are given in the *Supplement*.

The scientific sessions at Karachi strike a good balance between refresher teaching and new knowledge. The symposia will deal with conditions which will be of interest to doctors from all parts of the world, and the speakers will discuss the practical aspects of a range of common problems such as obesity, abdominal emergencies, and antenatal care. Some shorter sessions on the theme of "What's New" will present up-to-date information in fields such as the abnormal haemoglobins, where knowledge is advancing rapidly. The plenary session on "Planned Parenthood" has, perhaps, particular relevance for Asia and should provide a stimulating opening.

The social programme at Annual Meetings is always an added attraction for delegates, and many who will be visiting Pakistan for the first time will welcome the opportunity to see something of the country. Two evenings of music and dancing will give visitors an impression of the cultural heritage of Pakistan. Doctors from Pakistan have already made many friends for their country while working in Britain. The joint meeting gives British doctors the opportunity to strengthen the ties between the two countries.

¹ *Brit. med. J.*, 1966, 1, 997.

² Lehané, D., Kwantes, C. M. S., Upward, M. G., and Thomson, D. R., *Brit. med. J.*, 1949, 2, 572.

³ Mirick, G. S., Ward, R., and McCollum, R. W., *Vox Sang.*, 1962, 7, 125.

⁴ Duhanina, N. N., and Zukova, T. A., *Bull. Wld Hlth Org.*, 1965, 33, 853.

⁵ Lepeš, T., *ibid.*, 1965, 33, 856.

⁶ Tiburskaia, N. A., and Vrublevskaja, O. S., *ibid.*, 1965, 33, 843.

⁷ Bloch, O., *Bull. Johns Hopk. Hosp.*, 1941, 68, 412.

⁸ Wood, E. E., *Brit. med. J.*, 1955, 1, 27.