Parkinsonian tremor in most cases. Noradrenaline, as well as dopamine, is deficient in the brain in Parkinsonism, but neither noradrenaline precursors, which are thought to penetrate the brain, nor the α-adrenergic agonist drug clonidine have any useful therapeutic effects.[20]

The cause of idiopathic Parkinson's disease is not known. A viral aetiology, age changes in pigmented neurones, excess RNA synthesis, tyrosine hydroxylase deficiency, 3-OH-4-methoxyphenethylamine toxicity, heavy metal accumulation, and abnormal melanin metabolism have all been considered without convincing evidence of their role in pathogenesis.[21-27] There are four areas of dopamine neurones in the human brain—limbic, hypothalamic, medullary, and nigrostriatal—and only the last of these is damaged in Parkinsonism, which seems likely to be a disease of melanin rather than dopamine systems.[28] Lerner discovered melatonin (N-acetyl-5-methoxytryptamine) and showed that this pineal hormone induced sedation in man.[29] It antagonizes the darkening of the skin due to β-MSH, and initial results of treatment of Parkinsonism with melatonin were good.[30] However, control studies have shown that melatonin does not change the symptoms and signs of the disease and does not affect the anti-Parkinsonian action of levodopa nor levodopa-produced involuntary movements.[31 32] MSH by itself may aggravate Parkinsonian tremor, probably owing to its adrenergic effects.[33] Further studies of disease frequency in the white and coloured races of mankind, and the nature of brain melanin, may eventually give a clue to the cure of Parkinson's disease. Meanwhile, levodopa is the first miraculous treatment for the 60 000 to 80 000 people in the United Kingdom with this disease.[34]

1 *St. Luke*, ch. 13, vv. 11-13.
2 Vollmer, H., *Archives of Neurology and Psychiatry*, 1940, **43**, 1057.
3 Vicary, D. J., *et al.*, *Clinical Trials Journal*, 1973, **10**, 3.
4 Ogle, J. W., *Medical Times and Gazette*, 1865, **2**, 256.
5 Duvoisin, R. C., *Archives of Neurology*, 1967, **17**, 124.
6 Lebensohn, Z. M., and Jenkins, R. B., *American Journal of Psychiatry*, 1975, **132**, 283.
7 Berkeley, W. N., *International Clinics*, 22nd ser., 1912, **4**, 1.
8 Froment, J., and Mouriquand, G., *Revue Neurologique*, 1929, **2**, 547.
9 Kakunun, H., *et al.*, *Journal of the Japanese Society for Internal Medicine*, 1964, **53**, 354.
10 McCaul, J. A., Cassell, K. J., and Stern, G. M., *Lancet*, 1974, **1**, 735.
11 Gillhespy, R. O., and Mustard, D. M., *British Journal of Clinical Practice*, 1963, **17**, 205.
12 McGregor, C. C., and Priest, R. G., *British Medical Journal*, 1962, **1**, 114.
13 Wood, H. C., *Therapeutics*, 9th ed. Philadelphia, Lippincott, 1894.
14 Stefanis, C. N., and Issidorides, M., *Nature*, 1970, **225**, 962.
15 Miller, R. J., and Kelly, P. H., *Nature*, 1975, **255**, 163.
16 Davis, P. L., and Stewart, W. B., *Journal of the American Medical Association*, 1938, **110**, 1890.
17 Cotzias, G. C., *et al.*, *New England Journal of Medicine*, 1970, **282**, 31.
18 Calne, D. B., *et al.*, *British Medical Journal*, 1974, **4**, 442.
19 Owen, D. A. L., and Marsden, C. D., *Lancet*, 1965, **2**, 1259.
20 Tarsy, D., Parkes, J. D., and Marsden, C. D., *Archives of Neurology*, 1975, **32**, 134.
21 Brown, E. L., and Knox, E. G., *Lancet*, 1972, **1**, 974.
22 Lewis, P. D., *British Medical Journal*, 1971, **3**, 690.
23 Issidorides, M., *Brain Research*, 1971, **25**, 288.
24 Martin, W. E., *Lancet*, 1971, **1**, 1050.
25 Barrass, B. C., Coult, D. B., and Pinder, R. M., *Journal of Pharmacy and Pharmacology*, 1972, **24**, 499.
26 Parkes, J. D., *et al.*, *Lancet*, 1972, **2**, 1373.
27 Shuster, S., *et al.*, *Lancet*, 1973, **1**, 463.
28 Greenfield, J. G., and Bosanquet, F. D., *Journal of Neurology, Neurosurgery, and Psychiatry*, 1953, **16**, 213.
29 Lerner, A. B. *et al.*, *Journal of the American Chemical Society*, 1958, **80**, 2587.
30 Anton-Tay, F., Diaz, J. L., and Fernandez-Guardiola, A., *Life Sciences*, pt. 1, 1971, **10**, 841.
31 Papavasiliou, P. S., *et al.*, *Journal of the American Medical Association*, 1972, **221**, 88.
32 Shaw, K. M., Stern, G. M., and Sandler, M., *Lancet*, 1973, **1**, 271.
33 Cotzias, G. C., Van Woert, M. H., and Schiffer, L. M., *New England Journal of Medicine*, 1967, **276**, 374.
34 *Parkinson's Disease.* Studies of Current Health Problems, No. 51. London, Office of Health Economics, 1974.

Hormones and Elderly Testes

The normal pattern of human testicular endocrine function in old age has only recently become clear. Ten years ago reports suggested[1-3] that plasma testosterone levels did not change in men with advancing age though hormone production and metabolic clearance rates[2 4 5] and urinary testosterone excretion[6] diminished. Since then more extensive studies have shown a marked fall in plasma testosterone in normal men around the sixth decade,[5 7 8] though there is wide variation between individuals. Measurement of total plasma testosterone does not accurately reflect changes in the biologically active 1-2% that is not bound to protein. This falls more markedly in old age, because there is a concomitant progressive rise[5 7-9] in sex-hormone-binding globulin (S.H.B.G.) concentration after the age of 50. The rise in S.H.B.G. and increased binding accounts for the reduced metabolic clearance rate of testosterone. The mean unbound testosterone in extreme old age is around a third to a half that in young men.[5 7 8] There are conflicting reports on plasma oestradiol and oestrone levels in old men.[7 10-12]

There is now strong evidence that the reason for this modest decline in testosterone production and unbound plasma levels in old age lies in the testis. Mean levels of both L.H. and F.S.H. rise progressively from the fifth decade onwards[7 8 13 14] and are above the normal range for young men in more than half of those over 70, and in the castrate range[8] in 15-20%. The pituitary L.H. and F.S.H. response to synthetic gonadotrophin releasing-hormone is augmented,[7] while the Leydig-cell response to human chorionic gonadotrophin (as judged by a rise in plasma testosterone and oestradiol) is diminished.[5 12]

The testes become smaller in old age,[8 15 16] and spermatogenesis diminishes[17-19] as does the total Leydig-cell mass[15 20 21] after the age of 40. Though the reason for these changes is not clear the postmortem study of microvasculature of the testis by Sasano and Ichigo[15] suggested that changes in tubules and interstitial tissue might be secondary to vascular degeneration. The degenerative tubular and Leydig-cell changes are patchy and follow a pattern closely related to arterial supply; these focal changes are most marked in the posterosuperior part of the testis, which appears to be least well perfused.

A probable sequence of events, then, is that with ageing focal degenerative changes directly impair both spermatogenesis and production of testosterone by the Leydig cells. The fall in unbound testosterone is probably one factor that stimulates increased pituitary gonadotrophin production, but that cannot return testosterone production to heights enjoyed in youth. The level of S.H.B.G. (whose hepatic production is sensitive[22] to oestrogen-androgen balance) rises, the clearance rate of testosterone falls, and the pattern of testosterone metabolism changes to that seen in women or after oestrogen treatment.[5] If extreme androgen deficiency develops in old age the possibility should be considered of such conditions as Klinefelter's syndrome, in which the testosterone production falls much more than normal with ageing.[23]

Hitherto no detailed studies have related these normal hormonal changes of male senescence to well-being, sexual activity, gynaecomastia, or osteoporosis. Prostatic hypertrophy seems less marked in old men with declining testicular function,[8] and this may offset the possible disadvantages. In men with clinical evidence of androgen deficiency the levels of L.H., F.S.H., and total plasma testosterone should be measured (estimation of the bound level being largely a re-

search procedure). If gonadotrophins and testosterone are low, hypothalmic or pituitary disease is likely. If gonadotrophins are high and testosterone very low then androgen therapy is probably indicated, if only to prevent or treat osteoporosis. Until further research has been conducted the less extreme "normal biochemical abnormalities" of advancing testicular age should probably be left alone.

[1] Coppage, W. S., and Cooner, A. E., *New England Journal of Medicine*, 1965, **273**, 902.
[2] Kent, J. Z., and Acone, A. B., *Androgens in Normal Pathological Conditions*, ed. A. Vermeulen and D. Exley, I.C.S. No. 101, p. 31. Amsterdam, Excerpta Medica Foundation, 1966.
[3] Gandy, H. M., and Peterson, R. E., *Journal of Clinical Endocrinology and Metabolism*, 1968, **28**, 949.
[4] Lipsett, M. D., in *The Human Testis*, ed. E. Rosemberg and C. A. Paulsen, p. 407. New York, Plenum Press, 1970.
[5] Vermeulen, A., *et al.*, *Journal of Clinical Endocrinology and Metabolism*, 1972, **34**, 730.
[6] Vermeulen, A., in *Androgens in Normal Pathological Conditions*, ed. A. Vermeulen and D. Exley, I.C.S. No. 101, p. 71. Amsterdam, Excerpta Medica Foundation, 1966.
[7] Rubens, R., *et al.*, *Journal of Clinical Endocrinology and Metabolism*, 1974, **39**, 40.
[8] Stearns, E. L., *et al.*, *American Journal of Medicine*, 1974, **57**, 761.
[9] Anderson, D. C., *Clinical Endocrinology*, 1974, **3**, 69.
[10] Pirke, K. M., and Doerr, P., *Acta Endocrinologica*, 1973, **74**, 792.
[11] MacDonald, P. C., *et al.*, in *Control of Gonadal Steroid Secretion*, ed. D. T. Baird and J. A. Strong, p. 157. Edinburgh, Edinburgh University Press, 1971.
[12] Longcope, C., *Steroids*, 1973, **21**, 583.
[13] Schalch, D. S., *et al.*, *Journal of Clinical Investigation*, 1968, **47**, 665.
[14] Ryan, R. J., and Fairman, C., in *Gonadotrophins*, ed. E. Rosemberg, p. 333. Los Altos, Geron-X Inc., 1968.
[15] Sasano, N., and Ichigo, S., *Tohuku, Journal of Experimental Medicine*, 1969, **99**, 269.
[16] Hafez, E. S. E., in *Human Reproduction*, ed. E. S. E. Hafez and T. N. Evans, p. 193. New York, Harper and Row, 1973.
[17] MacLeod, J., and Gold, R. Z., *Fertility and Sterility*, 1953, **4**, 194.
[18] Andrew, W., *The Anatomy of Aging in Man and Animals*, p. 183. New York, Grune and Stratton, 1971.
[19] Vilar, O., in *Human Reproduction*, ed. E. S. E. Hafez and T. N. Evans, p. 193. New York, Harper and Row, 1973.
[20] Bishop, M. W. H., *Journal of Reproduction and Fertility*, 1970, Suppl. **12**, 65.
[21] Harbitz, T. B., *Acta Pathologica et Microbiologica Scandinavica*, (Section A), 1973, **81**, 301.
[22] Burke, C. W., and Anderson, D. C., *Nature*, 1972, **240**, 38.
[23] Paulsen, C. A., in *Textbook of Endocrinology*, ed. R. H. Williams, 5th edn., p. 346. Philadelphia, Saunders, 1974.

Research in General Practice

Restricted publicity sometimes deprives eponymous lectures and prize-winning essays of their due philosophical and educational potential. Fortunately the 1974 Butterworth Gold Medal Essay on the management of high blood pressure in general practice has not suffered this fate.[1] It deserves comment for two reasons. More obviously it takes an important area of clinical practice—raised blood pressure—and examines the complementary roles of screening and preventive medicine on the one hand and the more traditional curative or palliative approach on the other. Less obtrusively it demonstrates and discusses the increasingly important role of general practice and general practitioners in modern clinical research.

Dr. Julian Tudor Hart has been concerned with the study of blood pressure for over a decade, and it is no surprise that his essay of some 20 000 words represents a substantial and reasoned contribution to current thinking. In short, he argues that certain levels of blood pressure are associated with an excess mortality which may be reduced by an acceptable form of therapy. Because the key sign is inconstant, because its significance is still under study, and because it is symptomless, its presence must be actively sought before its secondary effects present. The place to do this is general practice, the person to do it the general practitioner, and the method to be used is a continuous screening programme based on a well-maintained age-sex register. Hart defines the at-risk levels of blood pressure in men as sustained 4th phase diastolic readings of 100 mm+ (age 20-39) and 105 mm+ (age 40-64); he sets the critical values for women 10 mm higher, though an addendum questions the validity of discriminating between them. Some 4% of patients are expected to fall into one of these categories, half being unknown to the doctor before screening.

While Hart is clearly right in asserting that a complacent attitude to this issue is no longer acceptable, it is far less certain that the case has yet been made for routine screening programmes for hypertension to be regarded as a necessary part of modern general practice. Probably no more than 1% of all patients will benefit and other groups—the obese, the smokers, the deaf, the unimmunized—will still compete for spare professional time and resources in the quest to improve the public health. As 90% of patients at risk visit their doctors spontaneously during a five year period—a similar figure to the attendance at a screening clinic—the maintainance of an up-to-date baseline blood pressure record by taking every opportunity to record it seems a fair compromise and a substantial advance over current practice.

The essay also draws attention to a second issue: the increasingly important role of the general practitioner in clinical research. As a relatively untapped field, general practice is widely and correctly regarded as the "North Sea" of research resources. But too few of the prospectors appear fully aware of the difficulties. Criteria of diagnosis and definition of terms are perpetual problems; the unravelling of the complex physical and non-physical determinants of illness behaviour another; and populations of consulting patients have to be seen as variable parts of the illness iceberg in different practices. The truth is that research workers using general practice populations are now realizing that research in general practice is in many ways more demanding and complex than it is in hospital medicine. If, as Hart suggests, "primary physicians of the future . . . are to . . . play as great a part in clinical and causal research as hospital physicians do now" an increasingly refined and professional approach will be required.

The present dilemma of general practice research is the conflict between quantity and quality—understandable in a relatively new specialty anxious to prove itself. This it already has done, and future developments must consolidate progress by favouring the careful study of well-defined and relevant clinical problems at the expense of large, superficially attractive exercises in data collection.

[1] Hart, J. T., *Journal of the Royal College of General Practitioners*, 1975, **25**, 160.

Antibiotics in Surgery

The place of antibiotics in surgery was the theme of a recent "panel by correspondence" in *Archives of Surgery*,[1] conducted by four American professors of surgery. Most surgical uses of antibiotics are prophylactic, and these have been the subject of much controversy, though the editor perhaps went rather far in classing prophylactic antibiotics with religion and sex as subjects which "should not be argued in polite company." The panellists' views on the drawbacks of such medication were predictable: they cited toxic and sensitivity reactions,