the oestrogen typical of the luteal phase of the cycle when it forms 50 per cent or more of the total oestrogen.

It has recently been shown (Rennels and Singer, 1970) that if immature female rats are treated with PMS/HCG (equivalent to FSH plus LH) ovulation occurs and corpora lutea develop. If a larger dose is given the corpora lutea become heavily luteinized, and at the same time the adrenals decrease in size. The authors demonstrate fairly convincingly that the adrenal suppression is due to output of DHA by the over-stimulated immature ovaries, the DHA acting as a negative feedback on the output of ACTH by the pituitary.

Girls who later develop anorexia nervosa reach menarche earlier than normal girls (Wright *et al.*, 1969), so perhaps the ovaries are not fully mature. If the steroid metabolism of the ovaries were analogous to that of the adrenals (which it is likely to be because embryologically they are derived from the same coelomic epithelium), one might expect that the route of synthesis of oestriol by these immature ovaries would be that of the foetal adrenals, namely: pregnenolone → 17OH → pregnenolone → DHA → DHAS → oestriol. In the case of the foetus the final stage is performed by the placenta. Presumably in the case of the ovaries this would be the role of the corpora lutea, which, from a chemical angle, have a function very similar to that of the placenta. If the corpora lutea were unequal to the task the result would be a condition analogous to that of the foetal adrenals at mid-term i.e. high DHA and low oestriol levels. The high levels of DHA might cause lanugo and also depress the adrenals. The latter might well cause anorexia, since anorexia is a symptom of Addison's disease.

Although anorexic girls have a number of symptoms found after adrenalectomy e.g. low blood pressure, bradycardia and inability to excrete a water load efficiently (Russell, 1965) they do not have all the symptoms of adrenal insufficiency. The simplest explanation would seem to be that they have a deficiency of *one* of the enzymes of the adrenal cortex, and that the adrenal depression (about 25 per cent in rats) is sufficient to put this enzyme completely out of action while leaving the others at the low end of the normal range.

It is well known that in man there is an interplay between the adrenals and the gonads. Thus, gonadectomy in both sexes leads to a rise in blood oestriol levels (Lemon, 1970) due to the adrenals. So the adrenals normally compensate for gonadal inadequacy in this way. On the other hand, adrenalectomy not infrequently leads to premature menopause in women as does also Addison's disease, so there are women who depend upon their adrenals for normal ovarian functioning. Presumably, in their case, the ovaries lack some substance (oestriol?) which the adrenals can provide.

If anorexic girls were in this position and had also an adrenal disorder leading to a deficiency of the substance required by the ovary, a vicious circle would develop. The inadequacy of the immature ovaries would lead to flogging by gonadotrophins from the pituitary; this would raise DHA levels which in turn would further depress the already inadequate adrenal enzyme. The most likely candidate for the adrenal enzyme would be one which takes part in the synthesis of oestriol.

This explanation of the illness has the advantage of being in accordance with the known genetic character of anorexia nervosa, which is rare and likely to be due to the inheritance of two mutant recessive genes. Generally, of course, such genes are at the same locus, which here they obviously could not be since one disorder is in the ovary and the other in the adrenal. However, if the two genes had the same function e.g. if both were involved in the synthesis of oestriol, the result might not be so very different.

GILLIAN M. SKUTSCH.

Biochemistry Department,
University College,
London, W.C.1.

REFERENCES

BIRCHALL, K., CATHRO, D. M., FORSYTH, C. C., and MITCHELL, F. L. (1961). *Lancet, i,* 26.
CRISP, A. H. (1965). *J. psychosomat. Res.*, **9,** 67.
LEMON, H. M. (1970). *Cancer,* **25,** 423.
RENNELS, E. G., and SINGER, E. L. (1970). *Texas Rep. biol. Med.*, **28,** 303.
RUSSELL, G. F. M. (1965). *Proc. Roy. Soc. Med.*, **58,** 811.
WRIGHT, W. S., MANWELL, M. K. C., and MERRETT, J. D. (1969). *Brit. J. Psychiat.*, **115,** 827.

MIGRAINE, ANOREXIA NERVOSA AND SCHIZOPHRENIA

DEAR SIR,

Dr. Avery, in his letter in the February 1971 issue of the *Journal* (Vol. 118 p. 255), has (as usual) missed the point I was trying to make in my own letter, which was that it seems unnecessary and unfair to deny the use of oral contraceptives, with their many obvious advantages, to all women who have a history of migraine. Quite often the migraine history will be associated with disturbances of sex-hormone balance, and it would seem reasonable to try to stabilize the levels by careful choice of an oral contraceptive. Obviously, most of us try to

avoid prescribing the high-dosage preparations which are most likely to cause troubles, anyway.

Incidentally, can anyone explain why it should be the oestrogen component that is thought to be responsible for thrombotic and embolic phenomena? It is common clinical knowledge that women are less liable than men to coronary thromboses while their oestrogen-levels are high in the reproductive phase of life, and that embolic episodes are most commonly associated with pregnancy and childbirth, i.e. high progestogen-levels. It therefore seems paradoxical to blame oestogens in oral contraceptives. I know about the statistical evidence, but where statistics and common-sense contradict each other I have no faith in statistics and want proper biochemical evidence to convince me.

PAULA H. GOSLING.

31, Arlington Road,
Eastbourne,
Sussex.

SCHIZOPHRENIA AND SEASON OF BIRTH

DEAR SIR,

Hare and Price (1969) report that there is a significant difference between the seasonality exemplified in the month of birth of 3,596 schizophrenic patients and of 14,076 neurotics admitted to the Maudsley Hospital during the period 1951–63. They suggest that the neurotic patients may be regarded as controls, and that therefore the month of birth of schizophrenic differs from that of the general population on the average.

The Registrar General (1961) has given quarterly live birth ratios expressed as percentages of the yearly ratios for each decade from 1841 to 1930 and each quinquennium since. Hare and Price give the age distributions of their neurotics and schizophrenics by five-year intervals. These patients were admited over a period of years centred on 1957. So one can calculate rough distributions by five-year intervals of the year of birth for these schizophrenics and neurotics. It is thus possible to compute the frequencies in each diagnostic category that would be expected to have been born in each quarter of the year on the hypothesis that there is no seasonality in the births of patients as compared with the population. For instance, during the decade 1891–1900 the ratios for the four quarters were 102, 102, 99 and 97. The numbers of days in the four quarters are 90·25, 91, 92 and 92. So the numbers of births in these quarters in that decade were in the ratios of $102 \times 90{\cdot}25 : 102 \times 91 : 99 \times 92 : 97 \times 92$. The four values shown in the top row of Table I distribute the 180 births for that decade in the ratio of these four numbers. The bottom rows of that Table give the numbers of schizophrenics observed to have been born in the four quarters and the numbers expected on the hypothesis that their births are distributed like those of the general population.

TABLE I

Frequencies of Schizophrenic Births in Each Quarter among Hare and Price's Sample of 3596, Observed and Expected on the Hypothesis that Schizophrenic Births are Distributed like the Births of the General Population

Interval	N	Quarter 1	2	3	4
1891–1900	180	45·37	45·75	44·89	43·98
1901–1910	360	90·75	92·40	90·69	86·16
1911–1920	647	164·69	164·45	161·37	156·48
1921–1930	1115	281·08	291·75	280·91	261·26
1931–1935	647	161·50	170·91	164·64	149·96
1936–1940	467	115·41	123·35	120·00	108·24
1941–1945	180	44·48	46·65	44·89	43·98
Expected	3596	903·28	935·26	907·39	850·06
Observed	3596	925	938	840	893

It will be seen that this technique too suggests that there may be a winter excess of schizophrenics—but it suggests that the peak incidence of schizophrenic births is in the fourth quarter rather than the first, as suggested by Hare and Price. It is not easy to interpret these data. If one tests the frequency of schizophrenic births in the fourth quarter against the sum of the frequencies in the other three, it is not significant. A χ^2 test of the frequencies in the two winter quarters (4 and 1) against the frequencies in the two summer quarters (2 and 3) is just significant at the ·05 level. However, there are reasons for questioning the mild suggestion provided by this result. As far as I know, only one set of published data (one of the distributions offered by Huntington, 1938) agrees with Hare and Price's material in indicating an autumn peak. Instead, most of the previous studies (Barry and Barry, 1961; Dalen, 1968; de Sauvage Nolting, 1934, 1954; four of the five distributions of Huntington, 1938; Laestadius, 1949; Lang, 1931; Norris and Chowning, 1962; Tramer, 1929) conclude that there is a preponderance of schizophrenic births in the spring; while a few others (Barry and Barry, 1964; Petersen, 1934; Pasamanick and Knobloch, 1960) have failed to detect seasonality.

I would conclude that the present data do not give as much support to the hypothesis of seasonality