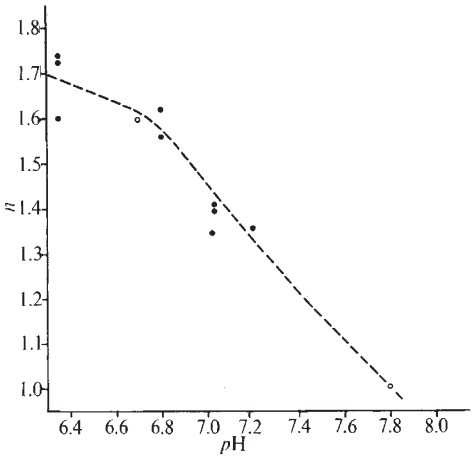

Fig. 4 Influence of *p*H on haem–haem interaction expressed as "*n*" of the Hill equation[27]. Phosphate buffers (I=0.1) Hb=0.63 mM. ●, Hb solution; ○, whole blood.

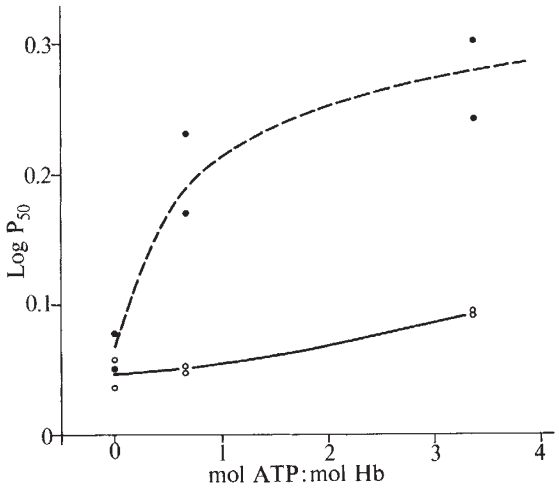

Fig. 5 Effect of ATP on oxygen affinity of *Latimeria* haemoglobin. Tris buffer, ●'s=*p*H 6.65, ○'s=*p*H 7.47, Hb=0.18 mM.

red cells of mammals[12,13] and nucleated red cells of birds[14], amphibians[15] and fishes[16,17]. The allosteric effect of organic phosphates is absent in the monomeric haemoglobins of cyclostome fishes[18,19]. The low *n* value of *Latimeria* haemoglobin with correspondingly low haem-haem interaction promised an interesting target for evaluation of organic phosphate effect on HbO_2 affinity.

The limited volume of whole blood available precluded measurement of red cell organic phosphate concentration. ATP, however, is known to be the major organic phosphate component in red cells of fishes[16,20], occurring in concentrations equimolar to haemoglobin. The pronounced effect of ATP on O_2 affinity of purified *Latimeria* Hb is shown in Fig. 5. As in other fishes[16] and mammals[21] the effect is more pronounced at lower *p*H.

The idea that a high HbO_2 affinity signifies a phylogenetically primitive condition has been advanced earlier by Wald[22] but strongly countered by Manwell[11]. HbO_2 affinity in fishes shows an indisputable relationship to oxygen availability in the ambient water, with O_2 deficient habitats correlating with higher HbO_2 affinities[23,24]. The O_2 content of the water at the depth of 200–400 m in the location where *Latimeria* have been caught is not known but studies in other tropical oceans have indicated that O_2 deficient layers are rather common. Whether the exceptionally high O_2 affinity of *Latimeria* haemoglobin is primitive or specialized must hence await further studies. It is evident, however, that if blood and tissue *p*H are within the normal range for other fishes, oxygen unloading at the tissue capillaries must occur under extremely hypoxic conditions.

The haemoglobins of lampreys and hagfishes give evidence to theories of haemoglobin evolution based on a monomeric ancestral haemoglobin[25]. The association of monomeric haemoglobins and subsequent evolution of quaternary structure basic to the Bohr effect and haem-haem interaction is fully manifest in high bony fishes whereas the elasmobranchs[26] and chondrostean fishes (K. J., Hansen and Lenfant, unpublished results), show absent or reduced haem-haem and a low haem–proton interaction. In this scheme *Latimeria* haemoglobin, a tetramer[27] with small haem–haem but large haem–proton interaction, is intermediate.

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Susceptibility to Cold in Newborns of Levodopa-treated Rats

Levodopa was developed for treating diseases of late maturity[1,2], but it is now being administered for diseases that occur during the child-bearing age[3]. Questions have arisen therefore about its effect on offspring. Observations were made on the offspring of rats treated with levodopa before mating or during gestation. Control mothers were treated with saline.

Sprague-Dawley virgin female rats weighing 200–250 g were caged in groups of three with one male at room temperature. Their mating was timed by the appearance of spermatozoa in the vaginal smear. Levodopa was given by daily gastric instillation. One day prior to estimated delivery, the rats were isolated for observation at 16–25° C. Mortality rates of the offspring during the first 12 hours after birth were recorded.

Inspection of offspring revealed a blue spot, which appeared a few hours after birth, between the scapulae of some newborn rats, with a much higher incidence in the offspring of mothers treated with levodopa during gestation, even in those treated on the first five days only. Levodopa has no effect when administered during the two weeks prior to mating. Most of the young with a blue spot were selectively cannibalized by both treated and untreated mothers and also by foster mothers. The blue spot itself was apparently not the signal for killing, because healthy newborns tattooed with a similar spot were nursed to weaning. Levodopa also increased the spontaneous mortality rate. Dissection revealed extensive subcapsular haemorrhages restricted specifically to the brown fat. Detailed macroscopic and microscopic examinations of the other tissues showed no abnormalities. Haemorrhages did not occur during intrauterine life (Table 1).

Table 1 Brown Fat Haemorrhage in Twenty-day Rat foetuses from Levodopa-treated Mothers

	% of foetuses with BF haemorrhage	No. of foetuses	No. of litters
Dopa 0.1 mg/g 1–10 day	0	33	3
Dopa 1 mg/g 1–10 day	0	39	4
Dopa 1 mg/g 1–20 day	1	34	3
Control	1	63	6
Total		169	16

Mothers were decapitated and foetuses were examined immediately. Note that haemorrhages were essentially absent during intrauterine life.

The brown fat surrounding the thorax of newborn mammals[4,5] is rich in both mitochondria[6] and microvacuolar lipids[7] and serves as the chief source of body heat[5,8] early in extrauterine life[9–11].

The brown fat does not become histologically visible until the eighteenth day of gestation[12].

Whether postnatal survival had been jeopardized by impairing the thermogenic contribution of brown fat was tested by placing representative newborns in the cold (10° C) until death (Fig. 1). Survival was reduced markedly in blue spot animals and to a lesser extent in the rest of the offspring of levodopa-treated mothers in comparison with those treated with saline. This suggests that the blue spot is a manifestation of an extreme form of some lesion in brown fat, promoted by levodopa. Histological comparisons were made therefore

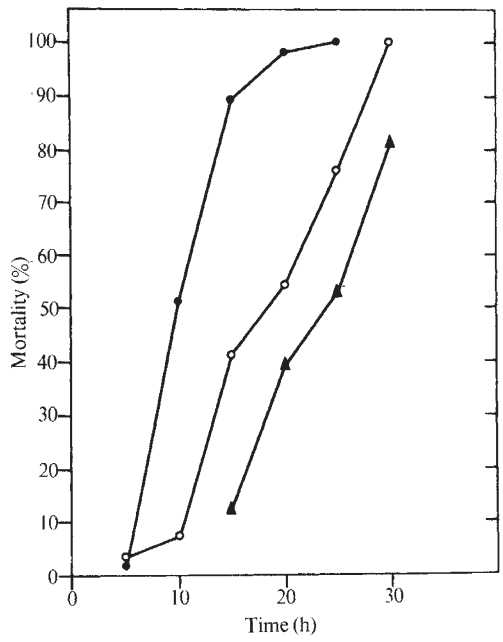

Fig. 1 Newborn rats 2–12 h old were placed in a refrigerator at a constant temperature of 10° C without their mothers. (Group 2, Table 2). Every 3–6 h they were removed for observations lasting 20 min and the survivors were returned to the cold. In six healthy control newborns kept at 22° C without their mothers, death occurred at 54 h. ○, Dopa 20 d; ●, haemorrhage; ▲, control.

	No.	Weight g	50% survey (h)	*P*
Dopa (22 days) haemorrhage	21	4.930	9.71 ± 2.35	< 0.001
Dopa (22 days)	119	5.974	18.70 ± 4.56	< 0.001
Control	48	5.927	23.77 ± 6.98	

between (1) control newborns from saline-treated mothers; (2) newborns with a blue spot from levodopa-treated mothers; (3) newborns without a blue spot from treated mothers; and newborns from treated mothers, exposed to the cold until (4) death. Paraffin sections were stained with hematoxylin and eosin and frozen sections were stained for lipids and glycogen. Experimental animals showed marked vasodilation with extensive haemorrhages in the brown fat of newborns in groups (2) and (3), microvascular lipids in the fat were depleted in all experimental animals, but to a greater degree in groups (2) and (3). There were no lesions in other tissues.

Evidence for metabolic interaction between levodopa and manganese[13–15] has been supported by the work of Cotzias *et al.*[16], who have shown an overlap in their transport systems. Levodopa (1 mg/g/day) was administered during the entire

Table 2 Brown Fat Haemorrhage in Newborn Rats from Levodopa-treated Mothers

Treatment	A % of newborns with BF haemorrhage	B % of offspring with early mortality	A+B	No. of animals	No. of litters
(1) Dopa 1 mg/g 1–5 day	14.7	1.6	16.3	61	5
(2) Dopa 1 mg/g 1–22 day	16.5	7.7	24.2	258	24
(3) Dopa 1 mg/g 1–10 day	14.8	6.5	21.3	129	14
(4) Dopa 0.1 mg/g 1–10 day	12.0	0	12.0	50	6
(5) Dopa 1 mg/g 15 days before pregnancy	3.2	0.7	3.9	140	14
(6) Dopa 1 mg/g 1–22 day $MnCl_2$ 0.2 mg/g	7.5	20.9	28.4	172	18
(7) Dopa 1 mg/g 1–22 day $MnCl_2$ 0.02 mg/g	3.7	7.5	11.2	53	5
(8) Dopa 1 mg/g 1–22 day Mn-deficient diet (milk)	28	53	81	51	5
Control	2.94	0	2.94	339	34
Total				1,253	125

Brown fat haemorrhage in experimental and control animals; for treatments 1, 2, 3, 4 and 8, $P < 0.001$; for treatment 6, $P < 0.05$; for treatments 5 and 7, *P* not significant.

pregnancy with and without manganous chloride to the regimen (0.02 mg Mb^{2+}/g/day). The incidence of haemorrhage in brown fat was greatly reduced by the addition of manganous chloride to the regimen (Table 2). The effect of manganese administration could be due to some change in the metabolism of levodopa. Administration of a manganese deficient diet of cow milk with levodopa (1 mg/g/day) markedly increased both incidence of bluespot and mortality of newborns (Table 2).

The experiments show that levodopa administration to rats during pregnancy can damage the brown fat. The selective cannibalization of such offspring by their mothers seems to be an indirect consequence of levodopa administration. Co-administration of manganese appears to have a preventive effect on the damage to brown fat induced by levodopa. These procedures offer a laboratory model for the study of defective thermoregulation in early life.

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Natural Regulation of Numbers in Primitive Human Populations

THERE are several possible mechanisms for the natural regulation of population size in animals[1], such as adjustment of the number of offspring per pair per season, the age of onset of sexual maturity, the percentage of adults reproducing, and the mortality schedules. The regulation of human populations might be achieved in similar ways; three demographic parameters which seem most amenable to adjustment: (i) the age at marriage, (ii) the interval between children, and (iii) the length

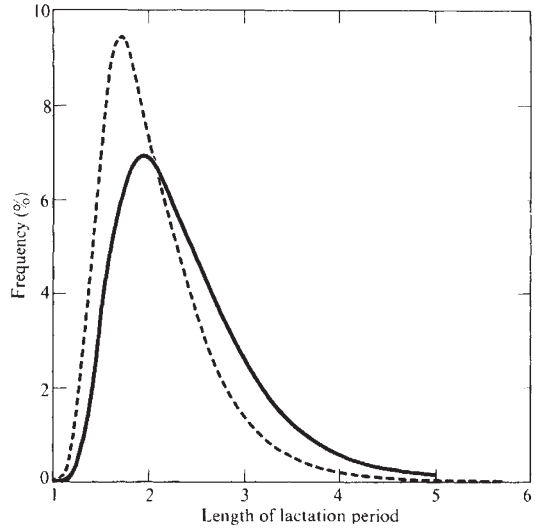

Fig. 1 Distribution of length of lactation period for $N=68$ (. . .) and $N=45$ (——). The means and variance of the lactation periods are 2.1 and 5.5 and 2.5 and 6.8, respectively.

of life. Here we discuss the way in which adjustment of the childspacing distribution can lead to effective population control.

We used a computer simulation program[2] constructed to incorporate age-specific fertility, and child-spacing was determined by foetal and infant mortality together with a period of sterility following a birth. This period of post-partum sterility might be due to taboos against coitus during lactation as occur in many populations[3–6], or to a physiological block to conception during lactation. It was possible to adjust the length of this period as a response to population size in the following way. For each 10-yr period we examined the number of marriages N, and adjusted the sterile period for marriages contracted in the next 10 yr. (Specifically we take the sterile period to be distributed as y where $y=(a+bN)x+c$, x being a lognormal variable[7], and c the minimum possible sterile period.) Fig. 1 shows the distribution of sterile period for $a=0.325$, $b=0.015$ and $c=1.0$ and two values of N.

The mechanism used to relate sterile period and population size is admittedly crude compared with what could be achieved in practice. But, as we shall see, the crude method used is sufficient to control population size, so any more refined method should be even more effective.

Four simulations were made of each of five distinct marriage systems appropriate to primitive man[8] (random marriage, two-clan exogamy, four-clan exogamy, four-clan cycling, and Kariera). For each system two runs were made in which no link between sterile period and number of marriages was made, and two runs were made with such a link. In every case the method of control proved effective. As an illustration we have plotted, for a four-clan patrilineal exogamous system, the number of marriages per 10-yr period against year. Fig. 2 shows the behaviour for the uncontrolled population, Fig. 3 the controlled population.

In the uncontrolled population the number of marriages per 10-yr period has increased during 600 years to 140, whereas in the controlled population the number of marriages per 10-yr period fluctuates between about 40 and 90 for over 1,200 yr. To achieve this measure of control over population size the mean sterile period has been adjusted only between 2.1 and 2.9 yr. These figures accord well with data on lactation period in the tribes with taboos on coitus during lactation[3–6], and the magnitude of the adjustment seems reasonable. Obviously if it were necessary to vary lactation period between 0 and 8 yr we should be extremely sceptical about its possible use in any populations. Such is not the case here, the mechanism seems both sufficiently strong to prevent population explosion or extinction, and yet sufficiently sensitive not to cause wild