J. Physiol. (1937) 90, 385-394 612.391.3:612-183

THE ROLE OF APPETITE IN THE CONTROL OF BODY WEIGHT

By N. F. MACLAGAN

From the John Burford Carlill Laboratories, Westminster Hospital Medical School

(*Received* 30 *April* 1937)

Our knowledge of the way in which the normal animal body maintains a fairly constant weight in spite of large fluctuations in energy intake and output is still very incomplete. The following factors are recognized by Du Bois [1936] as being concerned in this control:

A. *Under-nutrition* gives rise to (1) reduced basal metabolism; (2) reduced specific dynamic action of food; (3) lack of desire for exercise; (4) perhaps increased appetite. It may be noted that there is no scientific evidence for (4), which appears to rest on the fact that some experimentally under-nourished subjects feel hungry [e.g. Benedict *et al.* 1919]. It has not been demonstrated that they would eat more than their normal amounts if permitted. On the other hand, it is the usual experience of fasting men [Benedict, 1915] that no hunger is felt after the first few days of a fast.

B. *Over-nutrition* gives rise to: (1) Perhaps increased basal metabolism. The evidence for this is extremely conflicting, and particularly so in the case of human subjects. This question is of course bound up with the conception of "luxus consumption" introduced by Grafe in 1911. Recent work on this subject is reviewed by Du Bois [1936] who concludes that the existence of "luxus consumption" has not been adequately demonstrated. (2) Increased specific dynamic action of food. This is an increase affecting principally large protein meals, and would only take care of about 30 p.c. of the extra food taken. (3) Perhaps increased desire for exercise. This is merely a clinical suggestion, and hardly accords with one's feelings after a heavy lunch!

C. *Exercise* (under certain conditions) tends to increase the appetite. This is a matter of common experience but neither the mechanism

nor the quantitative aspects of this effect appears to have been investigated.

Further light on the problem may be sought in a study of those conditions in which the normal regulatory mechanism has broken down. The vast amount of experimental work on obesity has given mainly negative results, and Du Bois concludes that ordinary or exogenous obesity "is accompanied by no abnormality of metabolism striking enough to be demonstrated by our present methods". We are therefore forced to assume that obese persons simply eat more than they require, and this conception of obesity as an example of pathological appetite is at present gaining ground. The underlying cause of this increased appetite is unknown. Newburgh [1934] is inclined to a psychological explanation while Wilder [1932] suggests an "inherited hyper-irritability of the hunger centres".

In the opposite condition—unusual thinness in apparently normal persons—basal metabolism may be normal or slightly reduced, e.g. Blunt & Bauer [1922] found an average reduction of 1·9 p.c. in sixteen underweight college women. In patients seriously malnourished from any cause (excluding hyperthyroidism) all the changes listed under (A) above may be found [Lusk, 1921]. Now all these represent unsuccessful attempts to diminish weight loss, so that again the appetite emerges as the most significant factor.

If, then, the appetite is the most important factor in disturbances of body weight, it appears likely that it may be equally important in the normal control of body weight. Indeed it seems improbable that the metabolic changes discussed above could be produced by such small fluctuations in weight as must be effective if the observed facts are to be explained. Du Bois [1936] has made a calculation showing the extraordinary accuracy (0·05 p.c.) with which intake and output must be balanced in an individual who maintains a constant weight over a period of 20 years. Add to this the fact that an equal precision is displayed by different persons whose daily requirements may vary from 2000 to over 6000 kilocalories, and the notion of an uncontrolled or merely habitual intake appears to me untenable.

Appetite for the purpose of this paper is defined as the amount eaten in a standard time when an unlimited diet is presented, and has no direct relation to gastric motility or to subjective sensations, although it must of course be partly dependent upon these. It may be pointed out that appetite in this sense and hunger are not always directly correlated, e.g. it is well known that some persons feel hunger keenly but are satisfied by

small amounts of food, and the converse is no doubt common. In spite of the extensive literature on hunger, which dates principally from Carlson's [1912] and Cannon & Washburn's [1912] experiments, comparatively few papers could be found dealing with the measurement of appetite in the above sense.

Anorexia has been recognized for some years as the earliest symptom of avitaminosis B, the resulting loss of weight being the simplest method of detecting the onset of symptoms [Karr, 1920; Cowgill, 1921]. Anorexia was also produced in dogs by Rose *et al.* [1931] who restricted water intake until anhydræmia developed.

Graham & Griffiths [1931] described an unknown factor in autoclaved liver which was essential for normal appetite. The growth-stimulating property of liver when added to adequate purified diets was entirely due to stimulation of appetite [Johnson & Palmer, 1934].

A study on the effects of gonadectomy on rats had included measurement of the food intake with somewhat contradictory results. Thus Slonaker [1936] found an increased body fat in spayed animals, accompanied by a fall in food intake. He concluded that the castrates ate less and exercised less than the normals, thus retaining a higher proportion of the food ingested. Holt *et al.* [1936] found, on the other hand, an increased food intake in the castrates, and also an increased body weight, due not to fat but to general growth.

Clinical work on insulin therapy for increasing appetite in malnourished patients is also of interest, although no measurement of intake has usually been made in these cases. A good summary is given by Freyburg [1935], according to whose well-controlled experiments the effect is principally psychic. Three out of his eleven patients had, however, some gain in weight due to the insulin as such.

Experimental

In the present study the plan was to present an unlimited amount of food to rabbits for 6 hours each day, and to measure the actual amounts eaten in relation to physiological and pharmacological influences. Rabbits have certain advantages for this work because they eat methodically and fairly continuously, and are little affected by psychic influences. For example, if food be given to a rabbit immediately after a bleeding involving some struggling, it will start eating at once, and control experiments have shown that its appetite is quite unimpaired by any ordinary manipulation of this sort.

The food consisted of beet pulp, bran and water, mixed according to the directions of Mitchell & Pleasance [1927][1] and was placed in square cake-tins 6 × 6 × 3 in. which were clamped to the floor of the cage with detachable spring clips. The weight of tin plus food was made up to 600 g. at 11 a.m. when the experiment was started. The tin was then re-weighed at 12 noon, 2 and 5 p.m. One leaf of cabbage was then given to each animal and the food was removed, so that a fast of 18 hours was ordinarily imposed until the next feed. Either six or eight rabbits were used for each series of tests, of about 1–2 years of age, and weighing 2½–3½ kg. They were specially selected by previous trial, as a few could not be cured of the habit of food spilling. Most, however, took kindly to the tins and rarely spilt any food. Each rabbit was housed in a separate cage measuring 15 × 15 × 16 in., so that the amount of exercise possible was small and presumably fairly constant. In studying the effect of drugs, the "cross-over" method was used, i.e. four rabbits were given the drug and four the control injection of saline on 1 day, the injections being reversed on the next day.

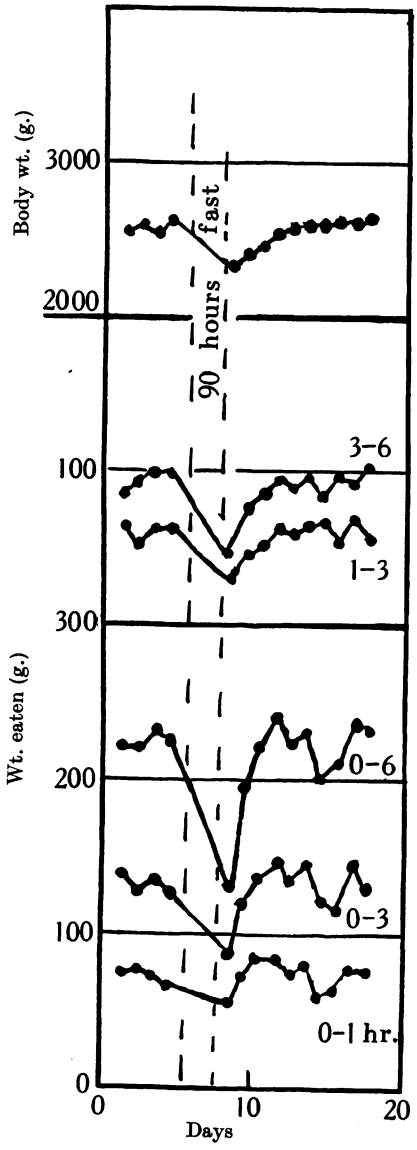

Fig. 1. The effect of a single 90 hr. fast on weight and appetite. Av. of 8 rabbits.

Length of fast. This was the first variable to be studied as it affected the design of the other experiments.

Fig. 1 shows the effect of a single

[1] This is now a standard diet for rabbits, and the animals appear to enjoy the food once they have become accustomed to it.

90 hours' fast, and it will be seen that this had the effect of depressing the appetite, for the first day, by about 50 p.c. using the 18-hour technique described above for the other days. The actual drop in appetite varied in the different hourly periods as follows:

0–1 hr.	−24 p.c.
1–3 hr.	−51 p.c.
3–6 hr.	−50 p.c.
0–6 hr.	−42 p.c.

The normal weight was regained in 5 days and the gain commenced immediately in spite of the impaired intake of food on the first day.

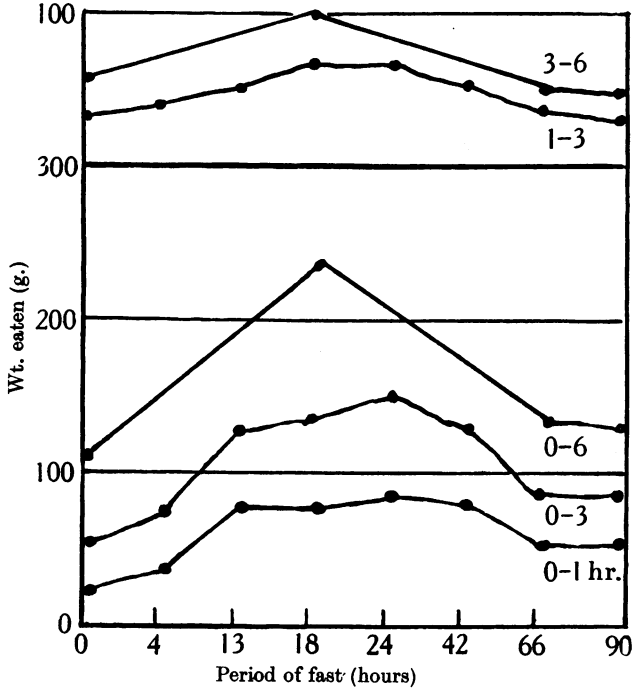

Fig. 2. The effect of varying lengths of fast on appetite. Av. of 6 rabbits.

Fig. 2 shows the relation between various lengths of fast and the amounts eaten. It is evident that the appetite reaches a maximum after 18–24 hours' fast, and is impaired either by increasing or diminishing this period. As a result of this experiment, and also as a matter of convenience, 18 hours was selected as the standard fast for subsequent tests.

Water was given *ad lib.* in all fasts of more than 24 hours.

Period of under-nutrition. In order to study under-nutrition without the disturbing effect of a long fast, the animals were kept on 100 g. of

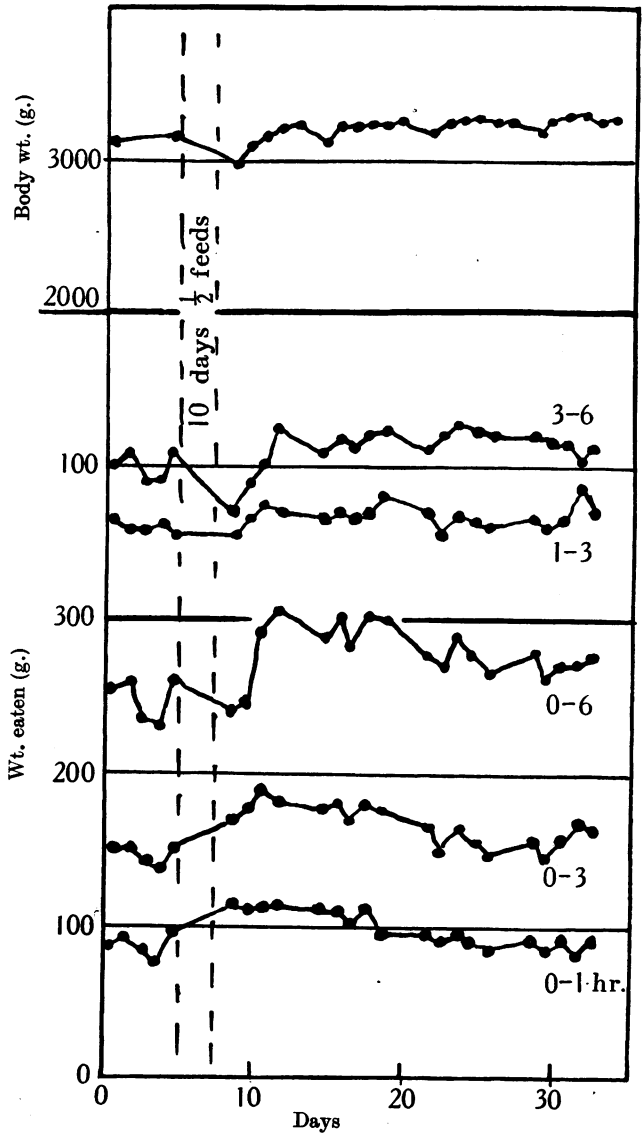

Fig. 3. The effect of 10 days on half rations (6 rabbits).

food per day (i.e. about half their usual amount) for 10 days, and then again presented with an unlimited diet. This produced a definite increase

of about 20 p.c., chiefly in the 0–1-hour feed, over the subsequent 8 days, while the previous weight was regained in 4 days (Fig. 3).

Drugs. Table I is a typical protocol of these results and illustrates the method employed. It will be seen from the table that 1 unit of "pitressin" (Parke Davis and Co.) produced a 31 p.c. decrease in the first hour's feed.

TABLE I. Effect of pitressin on amounts eaten (g.)

Rabbit no.	24 Sept. 1936			25 Sept. 1936			Differences		
	0–1 hr.	1–3 hr.	0–3 hr.	0–1 hr.	1–3 hr.	0–3 hr.	0–1 hr.	1–3 hr.	0–3 hr.
1	95*	60	156	101	70	171	− 6	−10	−16
2	62*	63	125	77	56	133	−15	+ 7	− 8
3	65*	74	139	89	60	149	−24	+14	−10
4	63*	58	121	82	65	147	−19	− 7	−26
5	91	76	167	60*	96	156	−31	+20	−11
6	62	72	134	34*	68	102	−28	− 4	−32
7	90	67	157	42*	91	133	−48	+24	−24
8	85	52	137	47*	63	110	−38	+11	−27
			Averages				−26	N.S.	−19
			Difference as p.c. of control feed				−31	0	−13

* 1·0 unit pitressin subcutaneously 15 min. before feeding. The remaining animals were given a similar injection of saline.

The statistical significance of the result is shown by inspection of the difference column, showing a change of the same sign and order of magnitude in each of the eight rabbits. In any case where doubt was felt on this

TABLE II. The effect of various drugs on the appetite

Drug	Dosage	How given	Effect as p.c. of control feeds		
			0–1 hr.	1–3 hr.	0–3 hr.
Insulin*	10 units	Subcut.	+ 7	+13	+10
Insulin plus glucose	5 units 10 c.c. 25 p.c.	,,	−11	−12	−11
Pitressin	5 units	,,	−81	0	−49
,,	1 unit	,,	−31	0	−13
Atropine sulph.	0·015 g.	,,	−70	0	−37
Ephedrine	0·5 g.	,,	0	−21	− 9
Enterogastrone	10 mg.	,,	−27	0	−13
,,	5 mg.	Intrav.	−27	0	−14
Glucose†	10 c.c. 25 p.c.	Subcut.	0	0	0
,,	4 c.c. 25 p.c.	Intrav.	0	0	0
Pitocin	5 units	Subcut.	0	0	0
Ant. pituitary‡	≡15 g. dry	,,	0	0	0
Ketodestrin‡	500 units	,,	0	0	0
Testicular extract‡	½ capon unit	,,	0	0	0
Benzidrene	1 mg.	,,	0	0	0
Normal saline	20 c.c.	,,	0	0	0

* Blood sugar 47, 57 and 62 mg./100 c.c. at 1, 3 and 5 hr. in control experiment.
† Blood sugar 173 and 138 mg./100 c.c. at 1 and 3 hr. in control experiment.
‡ These drugs were a gift from Messrs Paines and Byrne, Ltd., Greenford, Middlesex, to whom acknowledgement is due.

score, Fisher's [1932] "t" test was applied to the figures, and the result reported as 0 or N.S. if this test showed no significance.

Table II gives a summary of the results obtained with the other drugs.

Discussion

Information was particularly desired on three principal points.

First, is there any indication of a mechanism controlling the body weight through the appetite? I think that the results of the period of under-nutrition answer this question in the affirmative, for the appetite was increased by 20 p.c. above normal during just that period when the previous weight was being regained. As mentioned above, this result has been rather lightly assumed by many writers without any definite evidence, but if once established it should go far towards proving the importance of appetite in this connexion.

The effect of a single prolonged fast was in sharp contrast to this, for it impaired the appetite by some 42 p.c. over 6 hours for the first day. It is interesting to note that in spite of this the previous weight was regained in much the same time (5 days). Evidently in this type of experiment the metabolic adjustments referred to above (lowered basal metabolism, etc.) are of importance and the intake can be temporarily adjusted at a lower level with equal advantage to the animal. It is as though nature had anticipated the physician's advice to break a fast with small feeds.

Secondly, can any light be thrown upon the mechanism of the control by the exhibition of drugs? The effects of glucose and insulin are of special interest in view of the disputed relationship between hunger, gastric motility, and the blood-sugar level. According to the recent review and experiments of Mulinos [1933], gastric motility has no relation to normal spontaneous variations in the blood sugar, although it can of course be increased by insulin and this increase can be abolished by the administration of glucose.

It will be seen from Table II that glucose, even by the intravenous route had no effect on appetite. Insulin produced a small increase (+10 p.c.) in the first 3 hours which is in harmony with Freyburg's [1935] clinical results referred to above. The depressing effect of insulin plus glucose is suggestive of some general metabolic influence, perhaps storage of glycogen in the liver or central nervous system.

The effect of atropine and pitressin were not unexpected in view of their well-known effect on gastric motility. Ephedrine has also been

shown to delay stomach emptying [van Liere *et al.* 1936]. Negative results were obtained with pitocin, anterior pituitary, ketodestrin, testicular extract and benzidrene.

Enterogastrone, for a supply of which I am much indebted to Prof. R. K. S. Lim of Peiping, produced a definite impairment of appetite in the first hour. This substance is an extract of intestinal mucosa which contains the principle active in the inhibition of gastric secretion and motility by a fatty meal [Kosaka *et al.* 1932]. It was used in the dosage recommended by these authors (2–3 mg. per kg.).

Thirdly, is there any drug which is likely to be of clinical value in controlling appetite? Insulin is the only one on the plus side, and has already been widely used for this purpose. Its effects in these experiments were definite but not large, and this in spite of a dosage (10 units) which is nearly a convulsive one in a fed rabbit. Smaller doses were tried without effect. Pitressin and atropine had to be given in rather large doses to produce any effect, e.g. the former caused slight diarrhœa in three out of eight animals, and the latter gave full dilatation of the pupils in the dosage employed. The effects of enterogastrone are rather transient and the drug is not active by mouth.

Summary

1. Mechanisms possibly involved in the normal regulation of body weight have been briefly discussed, special stress being laid on the control of the appetite as the most important single factor.

2. Appetite is defined for the present purpose as the amount eaten in a standard time when an unlimited diet is presented to the animal, and is not intended to denote a psychological state. A study has been made of the appetite in rabbits with the following results:

(*a*) The appetite normally reaches a maximum after 18 hours' fast.

(*b*) It is increased above this maximum by a period of under-nutrition.

(*c*) A simple fast of longer (or shorter) than 18 hours reduces the appetite.

(*d*) The effects of various drugs upon the appetite have been studied.

It is a pleasure to express my thanks to Dr R. J. V. Pulvertaft for his advice and encouragement. I am also indebted to the John Burford Carlill Research Fund for financial assistance.

REFERENCES

Benedict, G. (1915). *Publ. Carnegie Instn*, No. 203.
Benedict, G., Miles, W. R., Roth, P. & Smith, H. M. (1919). *Ibid.* No. 280.
Blunt & Bauer (1922). *J. Home Econ.* **14**, 171. Cited from du Bois (1936).
Cannon, W. B. & Washburn, A. L. (1912). *Amer. J. Physiol.* **29**, 441.
Carlson, A. J. (1912). *Ibid.* **31**, 175.
Cowgill, G. R. (1921). *Ibid.* **77**, 420.
Du Bois, E. F. (1936). *Basal Metabolism in Health and Disease.* London: Baillière, Tindall and Cox.
Fisher, R. A. (1932). *Statistical Methods for Research Workers.* London: Oliver and Boyd.
Freyburg, R. H. (1935). *Amer. J. med. Sci.* **190**, 28.
Grafe, E. & Graham, D. (1911). *Z. physiol. Chem.* **73**, 1.
Graham, C. E. & Griffith, W. H. (1931). *Proc. Soc. exp. Biol.*, N.Y., **28**, 1086.
Holt, H., Keeton, R. & Vennesland, B. (1936). *Amer. J. Physiol.* **114**, 515.
Johnson, D. W. & Palmer, L. S. (1934). *J. Nutrit.* **8**, 285.
Karr, W. G. (1920). *J. biol. Chem.* **44**, 255.
Kosaka, T., Lim, R. K. S., Ling, S. M. & Liu, A. C. (1932). *Chinese J. Physiol.* **6**, 107.
Lusk, G. (1921). *Phsyiol. Rev.* **1**, 523.
Mitchell, W. A. & Pleasance, E. (1927). *Lab. J.* **6**, 165.
Mulinos, M. G. (1933). *Amer. J. Physiol.* **104**, 371.
Newburgh, L. H. (1934). *Ann. intern. Med.* **8**, 459.
Rose, W. B., Stucky, C. J., Mendel, L. B. & Cowgill, G. R. (1931). *Amer. J. Physiol.* **96**, 132.
Slonaker, J. R. (1936). *Ibid.* **93**, 307.
van Liere, E. J., Lough, D. H. & Sleeth, C. K. (1936). *J. Amer. med. Ass.* **106**, 535.
Wilder, R. M. (1932). *Int. Clin.* Series 1, **42**, 31.