

Sleep is for Tissue Restoration

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It is traditionally believed that sleep helps children grow and that it restores us after a hard day. The belief is now supported by some 50 reports showing that rates of protein synthesis or of mitotic division are higher at the time of rest and sleep, though in man it has only been well established for the most accessible of tissues, the skin (Fisher, 1968).

Medical thinking has not yet grasped that tissue healing may be accelerated by sleep. There persists an assumption that degradation and synthesis in tissues not only continue all the time (as they do) but that they are continually equal (which they are not), and upon this invalid assumption has rested much clinical research into protein metabolism. In reality, myocardial proteins of rodents, for example, are synthesised more during the daylight period when they rest and sleep (Rau and Meyer, 1975), and the same is true of epiphyseal cartilage (Simmons, 1968).

We shall consider why the balance between degradation and synthesis in tissues should vary so much with activity and rest, why it is that sleep with large EEG slow waves is 'worth more', and why, too, scratching by itchy patients at night tells us something about sleep's restorative properties. Only when those restorative properties can be measured shall we be able to assess the complaint of insomniac patients that sleep leaves them still exhausted. Actually the rectal temperature of poor sleepers does not fall as low (Monroe, 1967), which may mean relatively higher rates of degradation and, thus, less restorative sleep.

Several indirect indicators link sleep with synthetic processes. Growing infants sleep a lot. Wolff and Money (1973) found that a group of children of short stature had grown only one-third as fast at times of poor sleep as of good. Analyses across many animal species have shown a strong correlation between sleep duration and metabolic rate (Zepelin and Rechtschaffen, 1974). The higher the metabolism by day, the higher the relative degradation, and longer sleep could mean greater compensatory synthesis. In men, the customary individual duration of sleep correlates positively with the individual's waking body temperature, and thus, probably, with waking metabolic rate (Taub and Berger, 1976). Daily metabolism correlates highly with log body weight (Kleiber, 1961) and so does the amount of REM (paradoxical) sleep that individual men and women get (Adam, 1977).

SLEEP AND ITS HORMONES

There are two types of sleep that alternate, one named NREM, or orthodox sleep, and the other REM, or paradoxical sleep. Human NREM sleep is divided into four stages, according to the EEG. Stages 3 and 4 are called slow-wave sleep, or SWS.

The return of interest to sleep's restorative role came with the Japanese discovery of a link between SWS and the large nocturnal secretion of human growth hormone (GH) (Takahashi *et al.*, 1968; Honda *et al.*, 1969). The secretion depends upon the presence of SWS (Sassin *et al.*, 1969; Schnure *et al.*, 1971) and this itself indicates that sleep is a time that facilitates anabolic processes in man. Growth hormone stimulates amino acid uptake into tissues, promotes protein and RNA synthesis (Korner, 1965), and has wide interreactions, such as stimulating red blood cell formation indirectly through erythropoietin (Peschle *et al.*, 1972). It raises blood free fatty acids, whose subsequent degradation is a source of cellular energy (ATP), thereby saving amino acids from catabolism and increasing their availability for protein synthesis during sleep.

Corticosteroids stimulate protein catabolism (Ardeleanu and Sterescu, 1973; Friedman and Strang, 1966) and the nocturnal peak of GH secretion comes at that time in the 24 hours when corticosteroids are lowest. Consequently, there is even greater net protein synthesis during human sleep, as demonstrated by Rudman *et al.* (1973) who injected GH and found significantly greater nitrogen retention after a 2300-hours dose than after a dose at 0800 hours.

Three other sleep-dependent human hormones are known; prolactin (Sassin *et al.*, 1973), luteinising hormone and testosterone (Boyar *et al.*, 1974; Rubin *et al.*, 1976): all four promote anabolism.

SLOW-WAVE SLEEP FOR COMPENSATORY RESTORATION

Sleep seems to compensate for the degree of waking activity. After sleep-deprivation, men have extra SWS (Berger and Oswald, 1962; Williams *et al.*, 1964), and monkeys extra GH (Jacoby *et al.*, 1975). The longer the wakefulness prior to a nap, the more the SWS and GH (Karacan *et al.*, 1974). Even one hour of extra wakefulness during the night is followed by extra SWS and GH in the later night (Beck *et al.*, 1975). Extra exercise leads cats to have more SWS (Hobson, 1968), ordinary men get more HGH (Adamson *et al.*, 1974), and athletes greater amounts of SWS (Baekeland and Lasky, 1966; Shapiro *et al.*, 1975; Maloletnev and Telia, 1975; Zloty *et al.*, 1973).

Thyroid hormone increases degradation, and whereas hypothyroid patients lack SWS (Kales *et al.*, 1967), hyperthyroid patients have an excess of it and more GH (Dunleavy *et al.*, 1974). After days when normal men have had higher thyroxine secretion they get more SWS (Johns *et al.*, 1975). Acute starvation increases both SWS (MacFadyen *et al.*, 1973) and GH (Parker *et al.*, 1972; Karacan *et al.*, 1973) at a time when the latter's protein-sparing action would be of importance, while after chronic starvation an increase of SWS is associated with

Table 1. Mitoses maximal during the time of rest and sleep. (It is important to remember that this is during the light period in rodents.)

Species	Tissue	Reference
Ectodermal Tissues		
Man	Epidermis	Fisher (1968)
Rat	Epidermis	Halberg <i>et al.</i> (1965), Chekulaeva (1969)
Rat	Corneal epithelium	Sigelman <i>et al.</i> (1954)
Mouse	Corneal epithelium	Vasama and Vasama (1958)
Frog	Crystalline lens epithelium	Kuznetsov <i>et al.</i> (1972)
Rat	Pineal parenchyma	Renzoni and Quay (1964)
Rat	Anterior pituitary	Nouët and Kujas (1975)
Hamster	Cheek pouch epithelium	Brown and Berry (1968), Izquierdo and Gibbs (1972)
Rat	Lachrymal, parotid and submandibular glands	Vonnahme (1974)
Pregnant mice	Mammary alveolar epithelium	Echave Llanos and Piezzi (1963)
Rat	Lip epithelium	Bertalanffy (1960)
Rat	Buccal mucosa	Bertalanffy (1960)
Rat	Anal epithelium	Bertalanffy (1960)
Mesodermal Tissues		
Man	Bone marrow	Mauer (1965)
Rat	Epiphyseal cartilage	Simmons (1964)
Rat	Bone marrow	Clark and Korst (1969), Hunt and Perris (1974), Uryadnitskaya (1974)
Mouse	Bone marrow	Clark and Korst (1969)
Rat	Kidney tubules	Sharipov (1967), Saetren (1972)
Rat	Thymus	Hunt and Perris (1974), Kirk (1972)
Rat	Inner enamel epithelium, incisor teeth	Gasser <i>et al.</i> (1972)
Endodermal Tissues		
Rat	Liver parenchyma	Vonnahme (1974), Jaffe (1954)
Mouse	Liver	Barnum <i>et al.</i> (1958)
Mouse	Squamous epithelium of tongue and oesophagus	Burns <i>et al.</i> (1976)
Rat	Rectal mucosa after injury	Reeve (1975)
Rat	Gastric epithelium	Clark and Baker (1962)
Rat	Lung interalveolar septa	Romanova (1966)
Rat	Duodenum	Scheving <i>et al.</i> (1972)
Mouse	Duodenum	Scheving <i>et al.</i> (1972)
Mouse	Colon	Chang (1971)

tissue-rebuilding (Lacey *et al.*, 1975). As will be mentioned later, SWS will also be most strongly associated with anabolic repair because metabolic rate is then at its lowest.

The hormones of higher organisms are sophisticated additions to more primitive controls. Table 1 lists tissues in which there is a higher mitotic rate during the rest and sleep period of higher animals, but there could be added examples from the rest phases of lower organisms, in which the kind of hormonal mechanisms we have outlined could not be responsible. At the simplest level, the unicellular organism has rhythms of activity, with food-gathering, on the one hand, and, on the other, of assimilation with repair or reproduction. Rhythms abound in living systems and, indeed, spontaneous oscillations about a mean are inevitable in any system subject to feed-back control.

RHYTHMS AND THE ENERGY CHARGE

To sustain life an organism has to maintain a chemical composition that differs from its surroundings, and to do so it must expend energy. It must repair its structural molecules and it must reproduce, both activities involving biosynthetic, energy-using processes. The energy is furnished by the catabolism of food and fuel stores to yield ATP (adenosine triphosphate) and is released by cleavage of the terminal phosphate(s), leaving ADP or AMP (the adenosine di- and mono-phosphates). These energy-releasing reactions are enzymically coupled to synthetic reactions to supply the energy that drives them. The adenine nucleotides AMP, ADP and ATP accept, store and transfer chemical potential energy and constitute a link among all the cell's activities. These include the maintenance of chemical gradients (e.g. Na^+/K^+ pumps), active transport, and energy for motor activity. Hence, the adenine pool is a link between activity/inactivity rhythms and the catabolic/anabolic balance of the cell.

To achieve co-ordination, some universal, internal signal must operate to enhance or inhibit the cell's chemical activities, all of which can be broadly divided into energy-yielding (ATP-producing) reactions and energy-using (ATP-depleting) processes. It is the energy state of the cell that provides that signal. Its influence on metabolic pathways has been defined by Atkinson (1968), who proposed that the level of energy charge,

$$EC = \frac{ATP + ADP/2}{ATP + ADP + AMP},$$

varying within a range up to unity, determines the relative rates of flux through ATP-producing and ATP-depleting pathways. Lower values of EC favour ATP-producing pathways and higher values of EC promote ATP-utilising sequences.

The loci of control are regulatory enzymes that are sensitive to the levels of the adenine nucleotides and catalyse the irreversible steps in biochemical sequences.

Irreversible steps mean that the end-product of a synthetic sequence is not degraded by the reverse of the synthetic pathway and, hence, the rates of synthesis and degradation can be controlled by a single signal that modifies the activities of the regulatory enzymes in both synthetic and degradative pathways simultaneously. The EC level provides such a signal and affects these pathways in opposite ways. Degradative pathways yield ATP and so raise the EC of a cell. A higher level of EC then acts as a signal to reduce the rate of degradation. Synthetic pathways depend on ATP to drive them and are promoted by higher levels of EC. If EC falls, it is a signal to increase degradation and curtail synthesis as the system tries to restore a higher EC, which is thermodynamically more stable (Goldbeter, 1974).

The control enzymes have response curves with steeper slopes in the region of higher EC, and physiological values lie in the highly responsive, 'cross-over' portion of the graphs (Chapman *et al.*, 1971; Atkinson, 1970) where small changes in EC can disproportionately alter the relative rates of synthesis and degradation (Fig. 1). In addition, both types of EC response curves can be modified by the concentration of the biosynthetic end-product in such a way that if, for example, a synthetic end-product were in short supply, then the responsiveness to EC of the control enzymes in the synthetic pathway would be increased and synthesis enhanced (Fig. 2).

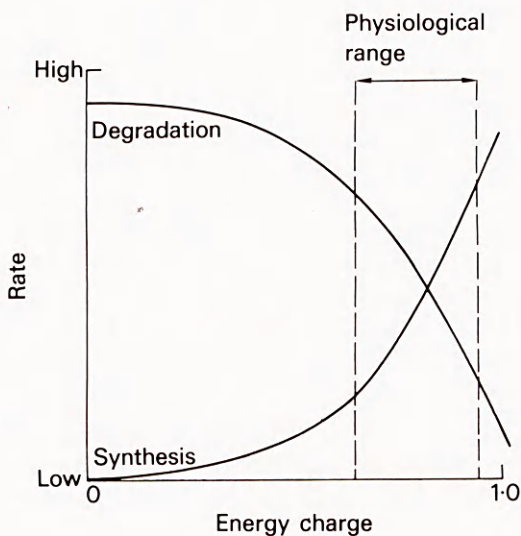


Fig. 1. In the physiological range small changes in energy charge have a big effect.

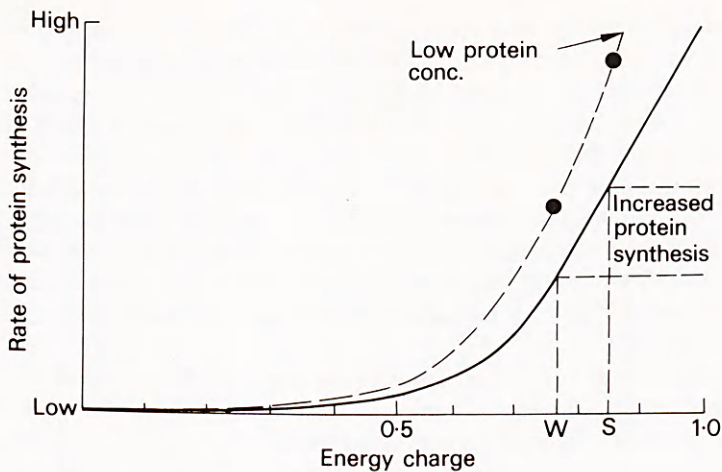


Fig. 2. The difference in energy charge between wakefulness and sleep may be small but it has a big effect – even bigger if end-product concentration is low.

Protein Synthesis, Growth and Activity

The concept of energy charge was originally applied to intermediary metabolism but the steps in protein synthesis, too, are sensitive to change in adenine nucleotides (Walton and Gill, 1975; Ayuso-Parrilla and Parrilla, 1975) and changes in EC are synchronised with growing and non-growing phases of *Escherichia coli* (Chapman *et al.*, 1971).

The simple organism's oscillations between rest and activity must induce concomitant fluctuations in EC and so, in turn, in other cellular processes. Motor activity demands ATP, so motility and food-gathering will lower EC, promote degradative processes, and temporarily suppress biosynthesis. During subsequent rest, the EC will rise and conditions become optimal for the biosynthetic processes previously curtailed, and these would be the greater with an added signal of low protein concentration.

Evidence that motility does inhibit synthetic processes can be seen in an experiment where the unicellular *Stentor coeruleus* was cut in half, such that each half received an equal share of the macronucleus, but only one half had the ciliary apparatus. Subsequent onset of mitotic activity took place much earlier in the cilia-free end (Guttes and Guttes, 1959); the EC must have risen during the enforced rest of the non-ciliated end and acted as a trigger for synthetic processes.

SYNTHESIS DURING REST IN HIGHER ORGANISMS

In complex organisms, motility and responsiveness to the environment are not characteristics of each cell, but the same principles apply. The house cricket,

Acheta domesticus, has a 24-hour rhythm of RNA and protein synthesis in its brain and sub-oesophageal ganglion, with synthesis highest when these insects are inactive. Their activity increases sharply with the onset of darkness, whereupon synthesis of RNA and protein in the brain falls to its lowest (Cymborowski and Dutkowski, 1969, 1970).

Higher organisms store fuel foods to allow prolonged activity without feeding. During such activity the energy-requiring biosynthetic pathways will be suppressed by a downward shift in the EC, which will stimulate catabolic processes in muscle. Additional tissues will be influenced by concurrent hormone release or, if their substrates for ATP production and synthesis of macromolecules are diverted, as fuel for motor activity.

In human muscle two minutes of exercise lowers ATP by 25 per cent (Karlson and Saltin, 1970) and in rat muscle EC and ATP likewise fall (Crabtree and Newsholme, 1972; Newsholme and Start, 1973; Wojciechowska *et al.*, 1975). Conversely, protein synthesis in rat diaphragm muscle (Robolledo and Gagliardino, 1971) and myocardium (Rau and Meyer, 1975) are higher during the resting/sleeping period. As examples of tissues linked indirectly, protein synthesis falls in the hypothalamus if rats exercise (Bordeianu and Butculescu, 1971) and protein synthesis in rat skin is at its highest during the daylight, when rats rest and sleep (Chekulaeva, 1969). In man, exercise inhibits skin mitosis for many hours afterwards (Fisher, 1968). Peaks in mitotic rate in frog crystalline lens epithelium coincide with episodes of motor inactivity, whereas troughs are associated with active periods (Kuznetsov *et al.*, 1972). It is important to distinguish such phenomena from the increased use of tissues that leads to their subsequent hypertrophy. The latter involves the activation of genetic material in the nucleus, with increased formation of RNA, and, subsequently, of proteins (Meerson, 1975).

Mitosis depends upon synthesis, whether for tissue maintenance or propagation of the species. There is a strong relationship between mitotic activity and higher concentrations of ATP (Guttes and Guttes, 1959). A fall in ATP below a critical level inhibits mitosis (Epel, 1963). A positive correlation between the rhythm of ATP level and cell division has been shown for *Tetrabymena pyriformis* (Plesner, 1964) and, as Table 1 showed, most tissues have a maximum mitotic rate during the resting/sleeping period, when ATP and EC levels must be highest. It seems that, through evolution, rhythms of mitosis have become entrained to the variations of energy state associated with the rest-activity cycle.

Human Sleep is More Than Rest

Rest reduces ATP depletion and so metabolic rate falls. Sleep is more than rest, it is a state of unresponsiveness brought about by active nervous mechanisms, a form of rest that ensures that the whole body, including the nervous system, can recuperate.

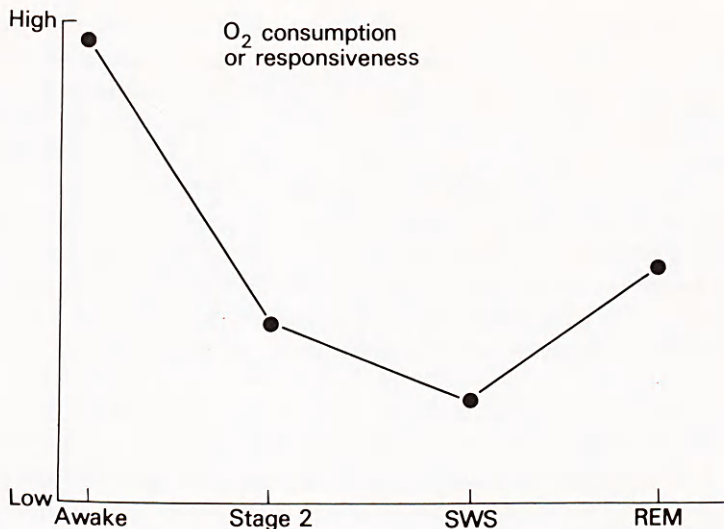


Fig. 3. In stages 3 + 4 (slow wave) sleep, responsiveness is lowest to auditory signals, scratching is least, blood pressure is lowest, and whole-body oxidative metabolism is lowest: the demands of cellular work, that compete with the needs of synthesis, are at their lowest.

The stages of human sleep differ in their degrees of unresponsiveness, with stage 2 being a less responsive state than wakefulness or drowsiness, and SWS a state of even lesser responsiveness, while REM sleep is about equal to stage 2.

These relationships in the degree of responsiveness are true for response to auditory stimuli (Williams *et al.*, 1966), blood pressure reflexes (Coccagna *et al.*, 1971), or scratching by patients with itchy skins (Savin *et al.*, 1975). Precisely the same relationships are true also of the metabolic rates that accompany these undisturbed sleep stages (Fig. 3). Human metabolic rate is some 10 per cent lower in stage 2 than in wakeful rest, with a further 2 per cent fall during SWS (Breibbia and Altschuler, 1968). Why it is that SWS is 'worth more' (Dement and Greenberg, 1966) can be understood in terms of the low metabolic rate (low cellular work) at that time, when lower oxygen consumption means less degradation, in response to higher EC, which, in turn, promotes a higher rate of protein synthesis. A 2 per cent margin does not seem large but one must remember that the events concerned are on the steep, highly responsive part of the curve in Fig. 2, where a small shift in EC leads to a disproportionate change in the rates of both synthesis and degradation.

SLEEP AND THE BRAIN

It is the brain that controls sleep and it is brain functions such as the power to sustain attention that are most obviously impaired by sleep deprivation. Although

the mature brain no longer grows, it still needs synthetic activity. It rivals the liver in its high rate of turnover of proteins and nucleic acids, consistent with its role in information processing, storage and retrieval, which rely on synthetic activity over and above the protein synthesis required for enzymes and renewal of structural components. The benefit of sleep is most obvious for the brain because during mere rest the nervous system remains responsive to the environment, whereas in sleep it becomes unresponsive (Steriade, 1970). The responsiveness of the wakeful cortex depends upon sustained ascending activation from the mesencephalic reticular formation, and the high levels of extracellular K^+ so caused (Katzman and Grossman, 1975). These higher levels of K^+ are closely coupled to higher energy consumption by the ATPase ion pump (Bachelard, 1975a; Jobsis *et al.*, 1975; Lowry, 1975).

Brain protein synthesis has its highest rates at the time when rats rest and sleep (Gordon and Scheving, 1968; Richardson and Rose, 1971; Rose *et al.*, 1969). The cat has several sleep periods and with each of these there is a rise in the protein content of perfusates from the brain (Drucker-Colin *et al.*, 1975). Jones (1971) found that brain ATP levels of golden hamsters were higher during sleep. The protein and RNA content of supraoptic nuclei was higher in sleeping rats than waking rats, while the latter, in turn, had a higher content than sleep-deprived animals (Doemin and Rubinskaya, 1974). Van den Noort and Brine (1970) measured the ATP, ADP and AMP concentrations in rat brain after 13 hours of sleep deprivation and after one hour of subsequent sleep. Calculations of EC using their results give a value of 0.77 after 13 hours of sleep deprivation but 0.83 after the one hour of subsequent sleep. This rise is in the highly responsive portion of the curve, and Fig. 2 illustrates how protein synthesis in the brain would differ under these two conditions and how there could be additional enhancement of protein synthesis during sleep at a time when end-product concentration would presumably be low, enabling us to understand why men who have suffered prolonged sleep deprivation can be restored by fewer hours of sleep than those they lost.

NREM-REM Cycles

The different physiology of NREM and REM sleep suggests that they differ in function, but a causal interrelationship has been proposed because NREM always precedes REM sleep (Hartmann, 1973). During SWS the majority of neurones have a much reduced firing rate compared with waking (McGinty *et al.*, 1974) and since activation from the reticular formation is at its lowest, ATP depletion would be reduced and the EC level would rise, whereas during subsequent REM sleep the higher firing rate (McGinty *et al.*, 1974) would be expected to lower intracellular ATP and stimulate brain glycolysis and respiration.

The amount of REM sleep has been thought to correlate with the required intensity of brain synthetic activity (Oswald, 1969, 1970, 1976; Stern and

Morgane, 1974). However, it is in REM sleep that skeletal muscles are at their most relaxed, and their ATP, EC and net protein synthesis must be maximal. If higher rates of brain protein synthesis were to occur during REM sleep itself in conjunction with the higher rate of cell-firing, this would imply compartments of ATP pools between, for example, neurones and glia, or intracellular compartments within neurones, as for glucose transport (Bachelard, 1975b).

In higher organisms, protein is synthesised at the rate of two amino acids per second, which means 1 to 2 minutes to synthesise a medium-sized protein molecule (Dintzis, 1961), in addition to the time required to initiate the process. Oscillations have been found in the rate of protein synthesis in a remarkable diversity of tissues (Brodsky, 1975). There is a theoretical minimum oscillation period of the order of minutes, because of the inertia in the protein synthetic machinery (Goodwin, 1963). The REM periods of most species last only a few minutes, and this is so short a time that the onset of a REM period could not be the primary initiator of any increased brain protein synthesis associated with that period, though peak rates of brain protein synthesis could coincide with the onset of REM periods. It is tempting to speculate with Brodsky (1975) that these oscillations in the rate of protein synthesis underlie NREM-REM sleep cycles.

CONCLUSIONS

It has been apparent for some years that sleep is a time that favours synthetic processes but previous communications (Oswald, 1969, 1976) had no biochemical base; the survey now presented has been refined by the first author, K.A.

It appears that the rest/activity cycle of simple organisms and the sleeping/waking rhythm of higher animals induce concomitant fluctuations in cellular work and, hence, in the cellular energy charge. As a consequence, metabolic balance alters so that degradative processes are stimulated during activity or waking, and restorative, synthetic processes are inevitably favoured during inactivity and sleep.

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MOTHER'S RUIN

The College sometimes takes pride in its eighteenth century opposition to the sale of gin. But two physicians started the whole business. In 1635 the royal physicians, Sir Theodore de Mayerne and Dr Cadyman, obtained from His Majesty a patent for 'the sole exercise of a new way of distilling strong waters and making vinegar out of cider, perry and buck whereof they are the inventors'. Two years later they joined up with other distillers of spirits, whisky, and geneva or gin to be granted a charter of incorporation as the Distillers Company. The gin trade was slow off the mark. In the year 1690 a total of 43,000 gallons was distilled, paying a duty of tuppence a gallon. By 1721 the output had risen to 2,800,000 gallons and many were worried that the common people were sodden with gin 'like opium with the Turks'. The College felt gin drinking had become a hazard to health and in 1725 petitioned the House of Commons for legislation to curb gin production having 'observed with concern for some years the fatal effects of several sorts of distilled spirits upon great numbers of both sexes rendering them diseased, not fit for business, poor - and too often the cause of weak feeble and distempered children, who must be instead of an advantage and strength, a charge to the country'. Perhaps as a result of this the government doubled the duty on gin and by 1741 the yearly output had risen to 7,500,000 gallons. It was Henry Fielding's prose and Hogarth's pictures that finally brought a halt to this alcoholic epidemic.