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REVIEWS

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R.M.S. must change. Its hitherto cocoon-like existence is fine for the forty or so active members, but the Society fails, even in its chosen rôle as an academic body, as it attracts by no means all of the best brains in the medical school. The Society must enlarge its sphere of activity and dispel its introverted and self-satisfied image. There are many who would be happy to see R.M.S. quietly fold up, believing that its roots lie well within its roots in the 18th century. However, I am sure that there is a place for a flourishing, undergraduate medical student society, especially one with the funds of R.M.S. The problem is how to make the R.M.S. flourish.

Many of the current objectives of the Society are pertinent and must be pursued, but others need to be added to make it relevant to medical students as a whole. The Society’s annual membership is about 120 and whilst it must be said that this is 50% up on five years ago, why are only one-seventh of Edinburgh’s medical students members of R.M.S., and equally important in the present context, why are so many of the more intelligent students spurned by our position in the student centre? Doubtless some of this latter group prefer individualised methods of study interspersed with complete relaxation, but there are many who decry the elitist attitude which has been propagated by some R.M.S. members. Their criticism is valid, but their resulting action is not.

The most effective way to change a small independent body is from within, but I will grant that even this is not easy in R.M.S. Such is the hierarchical structure of the Society that by the time one has got to a position of sufficient influence to try to effect change, one’s initial reformatory zeal has long worn off and one has become enmeshed in the R.M.S. way of life. It is important that people with new ideas and the drive to pursue them be encouraged to join and carry them out. This requires not only changes in the Presidential election system but also a more outward looking publicity and information system. Further, the organisational structure of the Society is such that the President is in no position to effect constructive change, but is entirely shackled by Council. This results in the anomalous position that the junior, but not the senior, members of Council have a sphere of influence in which they can operate entirely unchallenged.

One reason for not joining the Society is the £2.00 annual subscription. The Society’s activities are so structured that until one parts with £2.00 it is impossible to experience what you are going to get for the money. £2.00 will not deter those adamant that they wish to join, but to the unconverted this represents 12 pints of beer or 5 S.N.O. concert tickets, and is not to be parted with lightly. We failed narrowly last year in an attempt to reduce the subscription, but we will try again this year. Indeed I think abolition rather than reduction of the subscription will be necessary, at least by the time we enter our new building in Phase III, as I can see no other way in which all students will feel welcome. Only by encompassing the whole student body can there be any hope of dispelling the clique image which has been built up over so many years.

One of the major deficiencies of this medical school is the absence of a central common-room where students can sit and drink coffee or eat their lunch. I believe that this is one of the main reasons why students find the medical school so amorphous and lacking in any feeling of identity or community spirit. Our already disparate medical school is to be increased to 100 students per year, and this will exacerbate the existing depersonalisation which not only prevents full enjoyment of University life, but also acts as a disincentive to students performing to the maximum of their academic abilities. The University intends to put in a common-room in the new medical library in North George Square, but even when this eventually arrives it will be far too small to serve as the focus for medical student life. Some might say that there can be nothing worse than a totally medical student environment, and I would agree that as diverse a group of friends as possible is necessary, but when one is working it is pleasant to have somewhere to relax in comfort for a few minutes. This is one of the roles that I hope our new building will fulfill.

Our new premises will be in part of Phase III, which is the building now going up beside the Refectory and the Health Centre building. The layout of this building, with a large lounge area and several smaller working rooms will, I hope, leave the way open for R.M.S. to become more of a medical school coffee lounge and less of a library for a few dedicated workers. At present R.M.S. is seen as a place to work, as a means of getting into Ferrier’s lending library and as a place for weekly meetings on various medical topics. We must be seen to broaden our interests, as it will be essential for the Society to be an active and broadly-based student body or our position in the student centre will be rightly open to challenge.

A revamped R.M.S. could easily provide the services which medical student societies in other universities supply. It should become the meeting-place and provide the secretarial facilities for such groups as medic sports teams and year clubs. It should work more closely with the Medical Students’ Council, and dispel the mutual mistrust that separates the two bodies. They should both be serving the best interests of the medical student body, and they should therefore be in close touch with each other. A larger membership could also help the academic side of the Society. Instead of having one
meeting per week which necessarily does not attract
all medical students, there could be a number of
smaller meetings, perhaps utilising mainly Edinburgh
speakers, arranged by various groups within the
Society. For example, there could be groups on
renal medicine, gastro-enterology, etc., and there
could also be paraclinical and preclinical groups.
These latter two fields are ones in which the Society
fails at present to provide much of interest, as the
members, and especially those who are organising
such meetings, are predominantly from the senior
clinical years. In such a way a planned programme
of learning could be devised by groups of students
interested in a particular field, and although the
attendance at these meetings might be low the
benefit derived from them would be relatively large.
Such projects would not necessarily be more ex­
pensive than the present way in which the R.M.S.
organises its meetings but, even if it were, I feel
that this benefit derived by Edinburgh under­
graduates would be far greater than that obtained
from an elaborate R.M.S. Symposium like "The
Immunological Aspects of Cancer", which, although
an outstanding success from the prestige point of
view, benefited very few Edinburgh medical students
and cost £1,500.
I have perhaps painted a rather black picture of
the Society, which is in fact flourishing in its own
sweet way. Membership has risen this year, and,
far more important, attendance has been of a high
level. Our own library has grown and is about to be
supplemented by a tape-slide library for 24-hour use.
By this scheme, members will be able to freely
borrow tapes from the extensive Medical Recording
Service national tape-slide library for use on R.M.S.
equipment. Our Travel Scholarships are thriving and
many non-members have benefited from this
scheme. R.M.S. is under no moral obligation to
allow non-members to benefit from this money, but
I am glad that it is sufficiently outgoing to con­
tinue to do so.
These may be seen as faltering steps on the road
to improvement but the Society must change further
in order to become the forum for medical student
opinion. It must change its organisation, its role,
and its image, but I hope that it does not forget
that its prime objective is in the academic field.
The Society was created as a body for the self-
education of medical students and this is just as
pertinent now as it was in 1737.

THE SECOND BRANCH OF LEARNING

I. S. PALIN

"There are two branches of learning — religion and
medicine"
(Saying attributed to the Prophet Muhammad.)

Our society is peculiarly reluctant to acknowledge
any debt to its forebears other than those of defin­
itely western nature. Much is made of the Greek
and Roman origins of our ideas and ideals, while
the contribution of other, more eastern, societies is
usually omitted or glossed over in the course of
education and in no case is this better demon­
strated than in the case of our debt to the once
mighty and glittering civilization of the Moslems
Centuries of misunderstanding and resulting con­
flicts, culminating in the savage and bloody military
failure that was the Crusades, and the westward
surge of the Ottoman Turks who, by the late 17th
century had reached as far as Vienna and were
only narrowly repulsed, produced a torrent of pro­
paganda from both sides which even now obscures
the historical closeness of Christian and Islamic
societies and the role of Moslem learning in promot­
ing the great awakening that was the Renaissance.
It comes as a surprise to many to find that while
Europe was sunk into its "dark ages" there was a
civilization in the Middle East with a stability, culture
and level of achievement that the West was not to
know till the 18th century. The caliphs in Baghdad,
at the height of their power, ruled an empire of
which it was said that a virgin with a sack of gold
could walk from one border to the other without fear
of molestation. Their capital was not only a city of
glittering mosques and fountains, of paved and torch
lit streets, but a city of universities, free hospitals,
and public libraries. Islamic learning was so famed
that at least one of the Popes, Sylvester II, attended
a Moslem university to complete his education
before his elevation to the pontificate. Curiously
enough, of the great physicians of this period few
were Arabs, though the majority were Moslems. The
noted Avicenna (980-1036), and Rhazes (864-c.920)
were Persian, while Averroës (Ibn-Rushd), 1126-
1198, and Avenzoar (Ibn-Zuhr, 1109-1162) were
Moors, and the philosopher and scientist Maim­
onides (1135-1204), whose medical writings alone
would have been sufficient to ensure his immortality,
were Jewish by both race and religion.
The basis of Moslem medicine was in the classical
teachings to which they fell heir and added. Idn-
Sina (known in the West as Avicenna) is probably
the best-known of the Moslem physicians, parti-
cularly for his painstaking Qanun (Canon) of Medicine, an encyclopaedic work ranging through much of medicine and including an admirably clear description of skin diseases. But it was Rhazes, the impressively-named Abu-Bekr Muhammed Ibn-Zakariyya al-Razi, who was the greatest physician Islamic production, worthy to take his place with such immortals as Galen and Hippocrates in the medical pantheon. Born at Rayy, near Teheran, he established a continent-wide reputation for the scholarly and humanitarian practice of medicine, a profession he took up only in middle life. As head of the hospital in his native town he delegated much of the work to his pupils, and to the pupils of his pupils. New cases were admitted by those latter, who in difficulty would call in one of Rhazes, immediate pupils, or in particularly perplexing cases the great man himself. Invited to participate in the setting up of a new hospital in Baghdad, he had pieces of meat hung on strings in various parts of the city where land was available and sited the hospital where the meat had shown least signs of decomposition. Needless to say, he became the physician-in-chief of the hospital.

An example of Rhazes' clinical approach is given in his account of one of his own cases of a man with pyelonephritis:

"Abu'ddallah Ibn-Sawada used to suffer from attacks of mixed fever, sometimes quotidian, sometimes tertian, sometimes quartan, and sometimes recurring once in six days. These attacks were preceded by a slight rigor, and micturition was very frequent. I gave it as my opinion that either these accesses of fever would turn into quartan (i.e. would adopt a malarial pattern) or that there was ulceration of the kidneys. Only a short while elapsed ere the patient passed pus in his urine. I thereupon informed him that these feverish attacks would not recur, and so it was.

"The only thing that prevented me at first from giving it as my definite opinion that the patient was suffering from ulceration of the kidneys was that he had previously suffered from tertian and other mixed types of fever; moreover I did not at first come plain to me that his loins felt like a weight depending from him when he stood up, and I neglected to ask him about this. When he passed the pus I administered to him diuretics until the urine became free from pus. That the pus was evacuated quickly indicated a limited ulceration. The other physicians whom he consulted besides myself, did not understand the case at all, even after the patient had passed pus in his urine."

Rhazes' ethical teachings reveal him as a basically tolerant and rational man — perhaps too rational for some, since he regarded the idea of romantic love as something for "Bedouins, Kurds, and such-like clodhoppers", not for thinking and mature people. (In this he was echoed by Avicenna, who classed love as a "cerebral or mental disease" along with somnolence, insomnia, amnesia, mania, hydrophobia and melancholia). He anticipated by many centuries current health education campaigns by describing drunkenness as 'one of the evil dispositions that bring those indulging it to ruin, calamity and all kinds of sickness. This is because the excessive drinker is imminently liable to apoplexy and asphyxia . . . rupture of the arteries of the brain, and stumbling and falling into crevices and wells; not to mention various fevers, bloody clots, and bijous swellings in the intestines and principal parts, and delirium tremens and palsy, especially if there be a natural weakness of the nerves".

Rhazes' religious speculations — most of them now lost — were so unorthodox as to bring upon him the attacks of the Moslem clergy, and the cataracts which blinded him towards the end of his life were attributed to Divine punishment.

A curiously modern-sounding admonition to medical students of his time reads:

"And of those things which are incumbent on the student of this Art are that he should constantly attend the hospitals and sick-houses: pay unremitting attention to the conditions and circumstances of their inmates, in company with the most acute professors of medicine: and enquire frequently as to the state of the patients and the symptoms apparent in them, bearing in mind what he has read about these variations and what they indicate of good and evil".

Nor was the more experimental side of medicine neglected. In the 10th Century Al-Majdesi described the pumping action of the heart in some detail, and postulated communicating pores between the arteries and the veins, while the 13th Century Ibn-Al-Nalis described the pulmonary circulation and denied the Galenic theory of pores in the cardiac septum permitting the passage of blood. The two hypotheses thereupon concurrently flourished, some hundreds of years before William Harvey, the theory of blood circulation for which our histories still give the British physician credit.

An example of the standard of European medicine in the period we are discussing provides some comparison. A Saracen Emir, at a time of truce with the Crusaders then occupying the Holy Land, sent his personal physician, a Christian Arab named Thabit, to treat some of their sick, at the request of a Crusader lord. On his arrival Thabit found two patients, a man with an abscess in his leg and a consumptive woman, and commenced to treat the former by politicing, the latter by a suitable diet and herbs. Both began to progress but a Frankish doctor intervened, announced this treatment as useless, and turned to the man to ask him whether he preferred to die with two legs or live with one. Not unnaturally the man preferred the latter, whereupon the abscessed leg was amputated with such vigour that the man died almost at once. The doctor then decided that the woman was possessed of a devil in her head. Her hair was shaved off, her diet of fruit and vegetables was stopped, and she was fed instead on the normal Crusader diet of bread, garlic and oil: as she grew worse the Frank had a deep sign of the cross cut on her head, exposing the bone. Salt was rubbed in, but sepsis and death ensued. "I returned home", comments Thabit, 'having learned of their medical practice that which had hitherto been unknown to me'.

This is not to say that Islamic medicine was free of the mystico-religious outlook that helped hold back development of the art in Europe. The heretical sect of the Isma'ilis, who gave rise to the notorious secret society of the Assassins, were particularly active in this respect and would arouse the interest of potential converts with such questions as "Why has man seven cervical and twelve thoracic vertebrae?" and "Why has each of the fingers three joints but the thumbs only two?", various answers based on numerology being given. Modesty of the fact that the number of joints on the two hands was the same as the number of permanent teeth, the
number of days in the lunar month (which is used in the Moslem calendar) and the number of letters in the Arabic alphabet. Nonetheless, the evident erudition of Moslem doctors compared to their western counterparts was so great that the more progressive of Christian physicians appreciated what was translated from their writings. Chaucer's Doctor of Physick has no less than six Moslems in his list of authorities:

"Well know he the old Esculapius,
And Dioscorides, and else Rufus;
Old Hippocras, Hali, and Gallien;
Serapion, Rasis, and Avicen;
Avarrois, Damascene and Constantin;
Bernard, and Gatlsden, and Gilbertin".

Little wonder that Christian rulers who were in close communication with neighbouring Islamic states, as in partitioned Spain and in the Crusader-ruled Holy Land, used to send to the Moslems when they wanted a good physician!

I have attempted to give a brief outline of the debt our current medical practice owes to the great doctors of classical Islam, and in conclusion I cannot do better than quote from Meyerhof's authoritative work "The Legacy of Islam" —

"Looking back we may say that Islamic medicine and science reflected the light of the Hellenic sun when its day had fled, and that they shone like a moon, illuminating the darkest night of the European Middle Ages: that some bright stars lent their own light, and that moon and stars alike faded at the dawn of a new day — the Renaissance. Since they had their share in the direction and introduction of that great movement, it may reasonably be claimed that they are with us yet".

NOTE:

For those who wish to follow up this subject the writings of Edward Browne are recommended, who qualified in medicine, turned to Middle Eastern studies and went on to become Professor of Arabic at Cambridge. His scholarly work "Arabian Medicine" (C.U.P. 1921) is available from the Central Medical Library. The quotations in this article come from various sources and are translated either by Browne or by A. J. Arberry, the present Professor of Arabic at Cambridge University.

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NATRIURETIC HORMONE

HEATHER A. DAVIS

Until about 1957 it was generally accepted that the regulation of renal sodium excretion was dependent solely upon changes in
(a) glomerular filtration rate (Factor 1) and
(b) the activity of the renin-angiotensin-aldosterone system (Factor 2).

coupled with the effect of changes in intrarenal haemodynamics and physical factors, such as hydrostatic pressure surrounding renal tubules, and plasma protein osmotic pressure in peritubular capillaries.

Since that time, however, evidence has gradually been accumulated to suggest that these are not the only factors which are relevant in this context, and the existence of a humoral inhibitor of renal sodium reabsorption has therefore been postulated. This 'third factor' has been given the name of natriuretic hormone, and indications of its presence have been found in two principal situations. These are
(a) 'Sodium escape' during chronic mineralocorticoid administration
(b) Volume expansion with (i) isotonic saline
   (ii) blood

'Sodium escape' during chronic mineralocorticoid administration

When the extracellular fluid volume was expanded in healthy humans or dogs by chronic mineralocorticoid administration, an initial diminution of sodium excretion resulted, followed within a few days by a rise to control levels (2, 37). This 'sodium escape phenomenon' was attributed as early as 1957 to the existence of a circulating natriuretic hormone (37).

The presence of such a hormone was for some time disputed as many potential natriuretic factors have been identified during 'sodium escape' from chronic mineralocorticoid treatment. Other natriuretic factors include decreased plasma renin concentrations, increased glomerular filtration rate and increased renal plasma flow. Sodium escape has, however, been shown to occur in the absence of each of these variables, thus indicating that none of them is critical to the escape mechanism (see 8).

Recently, additional evidence for the existence of a circulating natriuretic hormone has been provided by Buckalew and Lancaster in 1972 (8). They demonstrated the presence of a substance with natriuretic activity in ultrafiltrates of jugular venous plasma when 'sodium escape' occurred in dogs undergoing chronic administration of deoxycorticosterone acetate (DOCA).

Volume expansion with isotonic saline

There is much evidence to suggest that when the blood volume of an animal is expanded with isotonic saline, the rise in urinary sodium excretion which...
occurs is due, in part, to a change in the concentration of a circulating hormone other than aldosterone. The release of such a circulating natriuretic hormone was postulated by de Wardener et al. in 1961 (43). They demonstrated that in dogs receiving high concentrations of vasopressin and mineralocorticoid hormones, an intravenous infusion of isotonic saline produced a rise in urinary sodium excretion even when the glomerular filtration rate was deliberately lowered by inflating a balloon in the thoracic aorta. A natriuresis also occurred in denervated and isolated kidneys perfused with blood from volume expanded animals. The tubular re-absorption of sodium must therefore have decreased, and this decrease must have been caused by some mechanism other than a fall in the concentration of aldosterone. Similar experiments and cross-perfusion (19) experiments involving volume expansion with isotonic saline have confirmed these results (see 42).

An interesting experiment was devised by Richet and Hornych (32). They saline-loaded rats, and demonstrated that sodium reabsorption was inhibited both in the renal tubules and in a piece of the in vivo perfused jejunum in each rat. Aldosterone pretreatment of the rats had no influence on this phenomenon. Since the two epithelial structures, which have common histological and immunological characteristics, were far apart, a natriuretic mechanism extrinsic to the kidney was postulated. They suggested that the natriuresis could have been mediated by a circulating hormone.

**Volume expansion with blood**

More precise evidence for the existence of a natriuretic hormone has been obtained from experiments in which the blood volume of animals was expanded with blood that was already in equilibrium with their own blood. Thus, haemodilution which is itself a natriuretic factor was excluded. A natriuresis was obtained using this method of volume expansion not only in whole animals but also in isolated kidneys perfused with blood from volume expanded animals. The volume expanded animals were treated with maximal doses of vasopressin and mineralocorticoid hormone and a natriuresis could be obtained even when the glomerular filtration rate was lowered (3, 20, 26, 39).

An elaborate experiment was performed by Tobian et al. (39) in which an isolated rat kidney was perfused with blood at a constant pressure (Fig. 1). The kidney’s only connection with the rat which supplied it with blood was the blood itself. When a quantity of a mixture of two parts blood and one part Ringer’s solution was placed into the venous reservoir without expanding the blood volume of the rat, there was no increase in sodium excretion by the isolated kidney (Fig. 1). When the same quantity of the mixture was infused intravenously into the rat and the blood volume expanded, there was in most instances a large rise in sodium excretion. This natriuresis was associated with a rise in renal blood flow and glomerular filtration rate. Since the rise in sodium excretion could not be attributed to haemodilution, renal nerve stimulation or a rise in arterial blood pressure, it was concluded that its cause must be a change in the concentration of a circulating substance which simultaneously increased renal blood flow by producing renal vasodilatation.

**Further evidence for the existence of a circulating natriuretic hormone**

This has been obtained from the detection of natriuretic activity in samples of plasma and urine. These samples were collected from volume expanded man and animals, and humans with various clinical conditions. Natriuretic activity has been detected in the following —

1. Plasma from saline-loaded dogs, rats, cats, sheep and cows (7, 9, 12, 31, 35) and plasma from dogs whose blood volume was expanded with blood (11, 30).
2. Plasma and urine from intravenously saline-loaded normal man and man on a high salt diet (10, 35, 36, 41). Also urine from orally water loaded humans (22).
3. Plasma and urine collected before and after saline loading of patients with primary aldosteronism (35, see 36).
4. Plasma and urine from saline loaded patients with essential hypertension (35).
5. Serum from uraemic patients (6, 7).
6. Plasma from dogs during nephron reduction (7).
7. Plasma from dogs (on a constant sodium intake) during ‘sodium escape’ as a result of chronic mineralocorticoid treatment (8).

Natriuretic activity has not however been detected in plasma and urine samples from humans on a low salt diet (35) or in urine collected from water loaded patients with congestive heart failure (22).
Assay preparations for the detection of natriuretic activity

Many in vivo and in vitro assay preparations have been developed for the detection of natriuretic activity in samples of plasma or urine. These are summarized below.

In vivo preparations

In most cases (6, 22, 35, 36, 41) the plasma and urine samples were concentrated and fractionated (using dialysis and ultrafiltration). Natriuretic activity was then detected in the samples by injecting or infusing them into assay rats and observing changes in urine flow and in sodium and potassium excretion from the bladder or ureters. The assay rats used in the different laboratories were under varying conditions of salt and water intake, and the samples were injected intravenously, intra-aortically, subcutaneously or directly into a renal artery.

Natriuretic activity has also been detected in un-concentrated plasma or dialysed plasma samples when they were injected directly into a renal tubule of an assay rat with hereditary diabetes insipidus. The rate at which the proximal tubular reabsorption of sodium was inhibited by the samples was determined by micropuncture (shrinking-drop technique) and by clearance techniques (31).

In vitro preparations

The transport of sodium, potassium and p-aminobenzoinic acid (PAH) has been studied in renal tubules fragments which have been incubated in vitro both in untreated plasma (11) and in concentrated and fractionated urine (10) taken from man and animals before and after blood volume expansion. When incubated in plasma or urine obtained after volume expansion, tubule fragments were less able to maintain a constant gradient of sodium and potassium, or to accumulate PAH than when incubated in control plasma.

Blood from blood volume expanded dogs inhibited the transepithelial transport of sodium by the isolated frog skin (30). Similarly, this preparation was used to detect natriuretic activity in concentrated and fractionated samples of uraemic serum (6).

Concentrated and fractionated plasma samples from saline loaded dogs, or dogs in which 'sodium escape' from chronic mineralocorticoid administration had occurred, inhibited toad bladder sodium transport (9).

Mode of action of natriuretic hormone

When natriuretic activity was detected in samples of plasma and urine using in vivo assay preparations, the natriuresis was accompanied by an increased renal blood flow, a factor which itself produces a natriuresis. From these experiments, it was, therefore, impossible to determine whether the postulated natriuretic hormone acted by a direct action on renal tubular sodium transport. The subsequent use of in vitro assay preparations for the detection of natriuretic hormone showed, however, that the hormone directly inhibited the cellular mechanisms for active sodium transport.

Thus, it is probable that natriuretic hormone acts in vivo both by directly inhibiting tubular sodium transport and by producing renal vasodilatation.

Site of action of natriuretic hormone

Micropuncture techniques have revealed that the fall in sodium reabsorption with volume expansion takes place in the proximal tubules (14, 31). Proximal tubular sodium reabsorption is also inhibited when the sodium escape' phenomenon develops in more prolonged experiments in which the extra cellular fluid volume has been expanded by the administration of mineralocorticoids (44).

It has been reported that the distal tubule plays no regulatory rôle in the control of sodium excretion (5, 42). However, once proximal tubular sodium reabsorption has been maximally depressed during the administration of a saline load, the rate of sodium excretion can still be increased (13). Thus, the inhibition of sodium reabsorption in the distal segments of the nephron is also important in regulating sodium excretion during saline loading, and natriuretic hormone may act in these segments (13, 34, 35).

Source of natriuretic hormone

Many ablational experiments have been performed in an attempt to locate the source of the proposed natriuretic hormone. Many of these experiments were misleading as saline administration to animals produces a fall in plasma protein osmotic pressure and usually a rise in arterial blood pressure. Both of these changes evoke a natriuresis even in an isolated kidney perfused by a heart lung preparation. Thus, it is not surprising that the administration of saline to a decapitated dog with the adrenals, liver and spleen removed, still produced a natriuresis (25).

Ablational experiments should, therefore, be performed using animals expanded with whole blood or blood with which their own blood is in equilibrium. Such an experiment, which was described earlier in this article, has been performed by Tobian et al., (39; see Fig 1). They suggested it was unlikely that natriuretic hormone was released from the adrenals or kidneys. Other workers have variously reported that natriuretic hormone could (19) and could not (33) be derived from the kidney. The liver (29, 38) and the brain (1, 12, 27, 37) have also been suggested as the source of the hormone. The origin of natriuretic hormone still remains uncertain.

Nature of natriuretic hormone

As a result of various attempts to detect natriuretic activity in plasma and urine samples, various reports as to the nature and properties of natriuretic hormone have resulted.

From studies using dialysis and gel filtration, the hormone has been reported to be non-dialysable and to have a molecular weight between 5,000 and 70,000 (35, 36). Other workers reported that the hormone was dialysable and had a molecular weight of less than 1,000 (6, 10, 12, 31). These conflicting results could readily be obtained if natriuretic hormone was a small molecule which was bound to a larger molecule (e.g. a plasma protein). In addition, natriuretic hormone has been variously reported to be a protein (35, 36), a polypeptide (12), to be resistant to boiling (8, 12, 35, 36) and to be stable only in the cold (31).

The natriuretic activity detected in some extracts displayed a delay in onset of up to one hour after injection and the effect lasted for up to three hours (35, 36). Again, these properties could suggest that natriuretic hormone was a small molecule which was slowly released from binding to a larger molecule. Other workers (31) however, found that their natriuretic material was rapid in onset (seconds),
with a short duration of action (less than thirty minutes). The hormone, which was effective on intravenous, intra-arterial or direct intratubular injection, has been reported to act primarily on sodium excretion and rarely to increase urine flow (31, 35, 36) but another report suggested that the hormone was more diuretic than natriuretic (12). The hormone produced an increase in renal blood flow (35, 36) but no change in potassium excretion or glomerular filtration rate. Natriuretic activity has been detected in both arterial and venous blood (31, 35, 36) but some workers were only able to detect the hormone in plasma samples which were concentrated before assay (6, 9, 10, 22, 31, 35, 36) whereas others detected it in blood or unconcentrated plasma (11, 12, 30, 31).

Some of the conflicting properties attributed to natriuretic hormone may result from the presence of contaminants in the plasma and urine extracts. Such contaminants could have been introduced during the concentration and fractionation procedures. In addition, bacterial endotoxins in urine samples have been shown to produce a potent natriuresis in assay animals (see Discussion after 36).

Natriuretic hormone and prostaglandins

It has been suggested that a prostaglandin could be a circulating (28) or intrarenal natriuretic hormone (23). Prostaglandins are a group of naturally occurring 20-carbon fatty acids which contain a cyclopentane ring and are derivatives of prostanoic acid (Fig. 2). Five series of naturally occurring prostaglandins have so far been described; namely the A, B, C, E and F series, all of which exhibit structural differences in the ring (Fig. 3). The prostaglandins possess a wide variety of pharmacological actions (18).

Prostaglandins of the A and E series have been shown to produce a natriuresis and diuresis in dogs and rabbits when infused in very low concentrations either intrasortically or directly into a renal artery (17, 28, 40, Davis, unpublished). Prostaglandin A1 produces a natriuresis when infused intravenously in concentrations as low as 0.001 and 0.6 nanograms per millilitre of arterial blood in dogs and rabbits, respectively. Since prostaglandins of the A series (unlike the E series) are not metabolised by the lungs, they also produce a natriuresis when infused intravenously in similar concentrations, and they could be capable of acting as circulating natriuretic hormones (28).

It has also been proposed that prostaglandins of the A and E series could be intrarenal natriuretic hormones, as prostaglandins A2, E2 and F2α have been identified in the renal medulla of the rabbit, dog and rat (see 23). Lee (23) has suggested that when the extracellular fluid volume is increased, prostaglandins A2 and E2 could be released from the renal medulla to circulate intrarenally (possibly via the vasa rectae or lymph) to the renal cortex where they could stimulate a natriuresis. This theory is supported by the observations that the enzymes responsible for the synthesis of prostaglandins exist in the renal medulla, whereas the enzymes responsible for their degradation have been detected in high concentrations in the renal cortex and not the medulla (see 23). However, it is also possible that during volume expansion, prostaglandin A2 could be released from the renal medulla into the renal venous blood, circulate and then produce a natriuresis by an action in the renal cortex.

The natriuresis produced by prostaglandins and natriuretic hormone is accompanied by vasodilatation in the renal cortex and an increase in renal blood flow. There is a redistribution of intrarenal blood flow from the medulla to the cortex. Glomerular filtration rate remains unchanged or increases slightly (see 23). It is not known whether prostaglandins stimulate a natriuresis in vivo solely by producing vasodilatation in the renal cortex, or whether they also exert a direct action on renal tubular sodium transport (18).

Since natriuretic hormone has been detected in samples of peripheral venous plasma, either a prostaglandin of the A series could have been detected or there is another circulating natriuretic hormone which either acts directly in the kidney to produce a natriuresis or stimulates the intrarenal release of prostaglandins of the A and E series.

Natriuretic hormone has also been detected in urine samples. Recently, prostaglandins E1, E2 and F2α have been identified in female human urine but no search was made for prostaglandins of the A series (15). Natriuretic activity in urine samples could, therefore, be attributable to the presence of prostaglandins of the E and possibly the A series.

Since the circulating concentration of prostaglandin A1 or A2 required to produce a natriuresis is very low and these prostaglandins are unstable in blood, no evidence for the release and circulation of these prostaglandins, during blood volume expansion, has yet been obtained (Davis, unpublished).

Clinical implications of natriuretic hormone

Natriuretic hormone has been associated with several clinical conditions, namely uraemia, aldosteronism, and congestive heart failure.

Uraemia

Since a natriuretic humoral substance was detected in the serum of uraemic patients, it was suggested by Bricker et al., (6, 7) that this hormone could serve in a homoeostatic rôle to increase the rate of sodium excretion per nephron as the number of nephrons diminished in advancing renal disease. Using experimental animals with nephron reduction, it has previously been shown
that the progressive natriuresis per nephron cannot be explained by a decrease in mineralocorticoid hormone activity, a change in glomerular filtration rate per nephron or by such physical factors as a change in cardiac output, mean arterial blood pressure, peripheral resistance or filtration fraction (see 5). It was also suggested (6) that in advanced renal disease, very high levels of natriuretic hormone could lead to the inhibition of sodium transport in extrarenal organs and contribute to the symptoms of the uraemic state.

**Aldosteronism**

Natriuretic activity was detected in extracts of urine and plasma samples collected, before saline loading, from patients with primary aldosteronism, but no such activity was detected in similar extracts from normal healthy humans (see 36). In addition, higher concentrations of natriuretic activity were detected in plasma and urine samples collected from saline loaded patients with primary aldosteronism than from normal humans (35, see 36). It is possible that in patients with primary aldosteronism, the enhanced basal and stimulated levels of circulating natriuretic hormone were released in order to offset excessive renal sodium retention produced by increased concentrations of aldosterone. This possibility is supported by the demonstration of a circulating natriuretic hormone in venous plasma taken from dogs during 'sodium escape' from chronic mineralocorticoid treatment (8).

**Congestive heart failure**

Krück (22) demonstrated that extracts of urine from orally water loaded humans possessed natriuretic activity, whereas similar extracts from water loaded patients with congestive heart failure possessed no such activity. He therefore suggested that an insufficiency or lack of natriuretic hormone in patients with congestive heart failure could be an explanation for the increased renal tubular sodium reabsorption and development of oedema in cardiac disease.

**Summary**

A considerable amount of evidence has now been accumulated to support the existence of a circulating natriuretic hormone. Natriuretic activity has been demonstrated in plasma and urine samples collected during volume expansion with isotonic saline or blood, the administration of a high salt diet, 'sodium escape' during chronic mineralocorticoid administration and in certain clinical conditions. Under these conditions natriuretic hormone is released in detectable concentrations, but lower amounts of the hormone may be released continually, to participate in the regulation of sodium excretion. The chemical nature of the hormone still remains unknown, but a prostaglandin of the A series could be intrarenal natriuretic hormones.

**ITEM OF MEDICAL INTEREST**

The next day, as Candide was walking out, he met a beggar all covered in sores, his eyes were sunk in his head, the end of his nose eaten off, his mouth drawn to one side, his teeth as black as a coal, snuffling and coughing most violently, and every time he attempted to spit, out dropt a tooth. (This was none other than Candide's old tutor, who described how he came to this state in these words)

"O my dear Candide, you must remember Pacquette, that pretty wench, who waited on our noble baroness; in her arms I tasted the pleasures of paradise, which produced these hell-torments with which you see me devoured. She was infected with the disease, and perhaps is since dead of it; she received this present from a learned cordelier, he was indebted for it to an old countess, who had it of a captain of horse, who had it of a marchioness, who had it of a page, the page had it of a Jesuit who, during his noviate had it from one of the fellow-adventurers of Christopher Columbus. For my part I shall give it to no-body for I am a dying man."

From Voltaire's "Candide", published in 1759.

**THERAPEUTICS PROBLEM**

A man attending an anti-coagulant clinic as an out-patient occasionally has unacceptably short prothrombin times. He claims to have been taking his tablets with religious regularity. He is rather surprised when the Doctor asks him what type of cooking oil his wife uses. Is this a relevant question? Answer on page 14.

Editor's note — A list of references provided by Dr. Davis is available from the Society's office.
INFECTION MONONUCLEOSIS AND E.B. VIRUS INFECTION

ELIZABETH EDMOND

The Disease

Infectious mononucleosis has long been an enigma to epidemiologists. The absence of a recognised casual agent or a specific diagnostic test has thrown confusion on such basic issues as the definition of the disease. Until recently the diagnosis has had to be based on a triad consisting of characteristic signs and symptoms, an absolute increase in atypical mononuclear cells, and a positive heterophile agglutination (Paul Bunnell test) test. Unfortunately each of these criteria is subject to variation in interpretation while the rigid application of the three allows no margin for the diagnosis of subclinical or atypical disease. Within these limits of diagnosis, work on the epidemiology of the disease has produced very few concrete results. While there is no doubt that infectious mononucleosis has a peak incidence in young adults and is relatively uncommon in childhood and older age groups, the evidence concerning infectivity, incubation period and methods of transmission has been circumstantial and often based on a small number of observations. Conclusions drawn from such work suggest that although the disease occasionally develops in contacts it is not highly contagious, and there remains doubt as to whether epidemics of the classical disease have ever occurred. Estimations of the incubation period range between very wide limits, and although there is some evidence that the causal agent is transmitted in saliva (hence the term "kissing disease") the method of natural transmission is still unproven.

Many of these problems of the behaviour of infectious mononucleosis could be solved if a specific causal agent could be recognised and during the last six years the accumulation of evidence implicating the EB virus has caused considerable interest amongst epidemiologists.

The Virus

The Epstein-Barr virus was described in 1964 when it was found to be present in cells cultured from a Burkitt Lymphoma. Its role in the production of the tumour remains an exciting controversial problem which cannot be dealt with here. All attempts to propagate the virus in other types of cell lines have so far been unsuccessful, and only human lymphoid haemopoietic cells will allow the virus to replicate. Antibody to the viral capsid antigen carried in the cells can be detected by an indirect immunofluorescence test described by Henle in 1966. Serological surveys using this technique showed that although antibody to the virus is present in all sera from patients with Burkitt Lymphoma, the antibody is also widely distributed in populations throughout the world regardless of the incidence of the tumour. Thus the incidence of EB viral capsid antibody in some student groups in Edinburgh is shown in Table I.

Table I Incidence of EBV antibody in healthy students

| Population           | Age | Sex | Year sera withdrawn | No. sera tested | % EBV antibody +ve. |
|----------------------|-----|-----|---------------------|-----------------|---------------------|
| 1st yr. P.E. College | 18  | F   | 1968                | 55              | 85                  |
|                      |     |     | 1969                | 40              | 90                  |
|                      |     |     | 1970                | 115             | 85                  |
| 4th yr. Medical Students | 21 | M & F | 1965                | 130             | 71                  |
|                      |     |     | 1970                | 122             | 64                  |
| University "Freshers" | 18 | F   | 1970                | 36              | 72                  |

Table II represents the age incidence of EB virus antibodies in hospital patients in Edinburgh. This is very similar to the age incidence reported from U.S.A., Scandinavia and England, and demonstrates that 32% of children already have antibody by the age of four years.

Age Incidence of Antibodies to E B Virus in Hospital Patients Edinburgh 1968 - 1970

| Age      | % EBV* |
|----------|--------|
| 0-3 months | 104    |
| 4-12 months | 54     |
| 13-24 months | 57     |
| 2-4 years | 65     |
| 5-14 years | 53     |
| 15-24 years | 52     |
| 25+ years | 55     |

Table II
In order to explain the universal occurrence and common pattern of age incidence of EB virus antibody, attempts were made to link production of this antibody with common infectious diseases. A chance occurrence in the Henle's laboratory in Philadelphia suggested that the antibody might be produced during the course of infectious mononucleosis. In conjunction with workers in Yale who had stored sera from patients with infectious mononucleosis for many years, they were able to demonstrate that sera taken from students before the onset of infectious mononucleosis were devoid of antibody while sera from the same students taken during the acute phase of the disease all had high titres of antibody to the virus. Furthermore, once developed, antibody to the virus persisted for many years, probably for life.

These findings have been confirmed and extended. Recent reports of the finding of macromolecular EBV antibody in the early stages of infectious mononucleosis and one report of the isolation of the virus from the throat of an acute case, make the case against EB virus almost watertight. Despite the doubtful ethics of the problem infectious mononucleosis has been produced on one occasion following injection of virus in a human volunteer.

There remain however many questions to be answered. In particular how is the virus spread?, can healthy carriers exist?, how much, if any, of the heterophile antibody negative disease is caused by EBV?, and what clinical syndromes other than classical infectious mononucleosis can be caused by infection with EBV? The fluorescent antibody test is positive in 80% of normal adults and therefore does not give a specific indication of disease — is the demonstration of EBV IgM antibody helpful in the diagnosis of atypical disease or can other specific tests of current infections be developed?

Edinburgh Student Virus Survey

It was with these unanswered questions in mind that the Edinburgh Student Virus Survey was initiated in October 1971. The survey was brought to the notice of individual students at the time of the matriculation chest x-ray and a sample of venous blood taken from volunteers, who also provided details of previous medical and social history. Sera were tested for antibody to EBV and as a service to female students also to rubella virus. Those students who remained seronegative were suspected of having infectious mononucleosis and one report of the isolation of the virus from the throat of an acute case, make the case against EB virus almost watertight. Despite the doubtful ethics of the problem infectious mononucleosis has been produced on one occasion following injection of virus in a human volunteer.

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Female students at Dunfermline College of Physical Education have been taking part in a similar survey started in October, 1970.

Results

Preliminary results of the first year of the survey are shown in Tables III - V.

A total of 613 sera were obtained from university student volunteers and 65% were found to possess antibody to EBV. There appears to be a higher sero-positivity rate in the female students.

Table III

| Sera Collected October, 1971 |
|-----------------------------|
| Nos. of sera screened | 322 | 281 | 613 |
| No. EBV antibody positive | 199 | 200 | 399 |
| % EBV antibody positive | 59.9 | 71.65 |

Table IV

| Results First follow up (May 1972) |
|------------------------------------|
| No. of 2nd sera available | 164 |
| No. EBV antibody positive | 18 |
| % Conversions | 11 |

Table V

| Incidence of Illness in Initial Seronegative Group |
|-----------------------------------------------|
| Group | Total No. | Proven or suspected I.M. | Other symptoms | No symptoms |
|-------|-----------|--------------------------|----------------|-------------|
| Sero-conversions | 18 | 5 | 6 | 7 |
| Persistent seronegatives | 146 | 0 | 54 | 92 |

After approximate seven months of academic life 18 of those students initially seronegative were found to have produced EBV antibody, giving a conversion rate of 11%.

Table V shows that of the 18 students known to have acquired EBV antibody in the seven months following their entry to university, 5 (25%) had been investigated as possible cases of infectious mononucleosis, while 7 (39%) had no symptoms of any kind. Other symptoms, mainly sore throats, were reported by 6. In contrast none of the 144 volunteers who remained seronegative were suspected of having infectious mononucleosis.

A small number of sera from patients in the acute phase of infectious mononucleosis have been investigated in this first year. It has been found that by the time the patient presents with symptoms, antibody to EBV measured by the fluorescence method is already present at high titre, and little change can be detected during the course of the illness. Antibody measured by the complement fixation reaction however appears to rise much more slowly and may not become positive until several months after the illness. If this is true then a combination of fluorescence antibody and complement fixing antibody may give a valuable indication of the timing of infection.

It is hoped that this, and many other aspects of the disease will be clarified in the next two years of the survey. The numbers involved at this stage are still small but in October 1972 a further 1,000 students have volunteered to take part. We would like to take this opportunity of thanking all our student volunteers and look forward to providing more details of the results at some future date.
MEASUREMENT OF BREATH-HOLDING TIME IN THE ACUTE RESPIRATORY PATIENT

DONALD F. GARDNER

Introduction:

In 1909, Douglas and Haldane (1) demonstrated the relationship of PaO2 and PaCO2 to breath-holding time (BHT). Muxworthy (7) described the direct effect of initial lung volume on breath-holding time in 1951.

At the present, it is felt that breath-holding time is determined by, "...the interaction of a number of independent variables which can be classified in two major sets of stimuli: those related to lung volume and those derived from changes in gas tension and pH." (3)

Although a considerable body of knowledge has been acquired about breath-holding in a laboratory setting, very little work has been done to date on breath-holding in a clinical setting with respiratory patients. It was the object of the present study to determine the feasibility of measuring BHT's on acutely ill patients in a clinical situation.

Another goal of this investigation was to study the hypothesis that breath-holding times would be longer in chronic bronchitics during periods of exacerbation than during periods of remission. This was felt to be true because of the decreased sensitivity to arterial CO2 manifested by these patients during periods of exacerbation. This was thought to be especially likely if any hypoxic stimulus could be eliminated by an inspiration to total lung capacity of pure O2 prior to breath-holding.

It was also felt that in chronic bronchitics during exacerbation, that increased importance of the hypoxic stimulus relative to the hypercapnic stimulus would be reflected in a greater ratio of BHT on air to that on O2 as the patient improved; that is, breath-holding times on O2 would be relatively longer during exacerbation when the hypercapnic stimulus was relatively weak.

In addition to chronic bronchitics several other types of respiratory patient were incorporated into the study. These included patients with pneumonia and asthma, and one patient with spontaneous pneumothorax. They were all chosen because they shared the characteristic of an acute illness which would be expected to show a good response to therapy and improvement in pulmonary function.

Methods:

Breath-holding times were measured daily at approximately the same time for each patient. A total of four BHT's was done each time, two following an inspiration to total lung capacity of air, and two following a similar inspiration of pure O2. Patients were instructed to inspire maximally to total lung capacity from an unmarked rubber bag containing air or O2 and then to exhale to a spontaneously chosen lung volume most comfortable to them (an approximation of functional residual capacity). Timing was begun by an observer at this point and continued to breaking point. Nose clips were kept on throughout the procedure. Breath-holds on air were alternated with those on O2, and the order of gases was changed each day.

Peak expiratory flow rate (PEFR) was also measured daily at the same time as the breath-holds on a Wright Peak Expiratory Flow Meter.

Arterial blood gases were drawn on days one, seven, fourteen, and/or day of discharge in patients with abnormal blood gases, and more frequently if the clinical situation warranted. No attempt was made to draw blood at the exact time of breath-holding, only during the afternoon of the same day.

Results:

Breath-holding times were obtained on a total of twelve patients. Of these, five had exacerbations of chronic bronchitis, three had bacterial pneumonia, three had acute exacerbations of asthma, and one had spontaneous pneumothorax.

There is an excellent correlation of mean breath holding time after a breath of air to that after a breath of O2 in all patients (Fig. 1). Likewise, as has been demonstrated by other observers (5), mean BHT on O2 was significantly longer than on air in all but one patient (Jon).

No patient with chronic bronchitis showed a decreased breath-holding time on air or oxygen with improvement of clinical status or pulmonary function or length of hospitalization.

The author regrets that an adequate number of blood gas analyses as recommended by the protocol...
could not be made on all patients for technical and other reasons. In those patients in whom several blood gas analyses were made, no correlation between BHT and arterial blood gas concentrations drawn on the same day could be determined.

In three patients with chronic bronchitis who showed significant improvement in mean BHT, two, (Jon) and (Mail), had an increased PaCO2 drawn on the same day, and one, (Mur), was unchanged. Two, (Mur) and (Jon), had an increased PaO2 as would be expected, but one had a decreased PaCO2 (Mau). Likewise, in six other patients who showed significant improvement in mean BHT no correlation between mean BHT and arterial gas tensions could be determined.

No general correlation could be shown between mean BHT and length of hospitalization. In the six patients who demonstrated a correlation between PEFR and mean BHT, only one (Ser) showed a good correlation between mean BHT and days of hospitalization and three, (Gif), (Max), and (Jon), showed no correlation between these parameters. Of the other six patients in the study, two did show a correlation of mean BHT with length of hospitalization and four did not.

No correlation could be shown between the ratio of mean BHT on air to that on O2 (mean BHT-air/mean BHT-O2) and mean BHT. Two patients, (Dru) and (Mur), showed a decrease in mean air/mean O2 as the mean BHT increased and one patient (Ess) showed an increase in mean air/mean O2 as mean BHT increased.

There was a failure rate of 19% due to the voluntary withdrawal of three patients from the experiment. One patient had to be withdrawn because of worsening clinical status.

Discussion:

This study has demonstrated that BHT can be measured in a practical way at the bedside and is of potential usefulness in the clinical setting. It must be recognised that breath holding does require a large degree of patient co-operation and is therefore excluded in the extremely ill, stuporous, or uncooperative patient.

Evidence has been obtained which suggests that there is a correlation of mean BHT on air and O2 to PEFR (and hence to airways conductance) in patients of all types who, (1) have airways obstruction upon admission, and (2) have significant change in airways resistance during therapy. Such a relationship might be explained by the length-tension inappropriateness hypothesis of Campbell for the etiology of dyspnea (4). More study is needed in this area with a larger number of selected patients.

Breathholding times in chronic bronchitics with elevated PaCO2's did not decrease with clinical improvement and no correlation between breathholding times and arterial PCO2 and PCO2 drawn on the same day could be demonstrated. Therefore, the original hypothesis that chronic bronchitics with elevated PaCO2 and a decreased sensitivity to arterial PCO2 would have longer breath holding times than during periods of remission could not be supported.

Since no correlation of the ratio of BHT's on air to those on oxygen could be shown with either mean BHT or PEFR, it could not be demonstrated that the hypercapnic stimulus to respiration became more important relative to the hypoxic stimulus with improvement in patient respiratory function.

The author is especially indebted to the ideas and help of Dr. G. J. R. McHardy of the pulmonary physiology section of the City Hospital, Edinburgh, and to the Medical Student Council of the University of Edinburgh for making the Edinburgh-Illinois student exchange possible.

Summary:

Breath-holding times were measured daily during an acute phase of illness in twelve patients with different types of respiratory disease. A direct correlation between airways conductance as measured by the peak expiratory flow rate (PEFR) and
mean breath-holding time was suggested. No relationship could be shown between breath-holding time and arterial blood gas concentrations taken on the same day. It was demonstrated that breath-holding time can be measured and may be useful in the clinical situation.

References
(1) Douglas, C. G., and J. S. Haldane. The regulation of normal breathing. J. Physiology, London 38:420-440, 1909.
(2) Mithoefer, J. C., C. D. Stevens, H. W. Ryder, and J. McGuire. Lung volume restriction, hypoxia, and hypercapnia as interrelated respiratory stimuli in normal man. J. Appl. Physiol 5:797, 1953.
(3) Mithoeffer, J. C. Breath-holding. Handbook of Physiology, American Physiological Soc. Section III, vol. II 1011-1025, 1966.
(4) Campbell, E. J., M., and Howell, J. B. L. The sensation of breathlessness. Br. Med. Bull., 19, 36-40, 1963.
(5) Engel, G. L., E. B. Ferris, J. P. Webb, and C. D. Stevens. Voluntary breath-holding. I. The relation of the maximum time of breath-holding to oxygen tension of the inspired air. J. Clin. Invest. 25:729-733, 1946.
(6) Fowler, W. S. Breaking point of breath-holding. J. Appl. Physiol. 6:539-545, 1954.
(7) Muxworthy, J. F. Breath-holding studies: relationship to lung volume. Air Force Technical Report 6528, pp. 452-456. Ohio: Wright-Patterson Air Force Base, 1951.

ITEM OF MEDICAL INTEREST
22d. To the Crown Tavern behind the Exchange, and there met the first meeting of Gresham College since the plague. Dr. Goddard did fill us with talk in defence of his and his fellow physicians going out of town in this plague time; saying that their particular patients were most gone out of town; and a great deal more etc. But what, among other fine discourse pleased me most was Sir G. Ent, about respiration; that it is not to this day known, or concluded upon among physicians, nor like to be done either, how the action is managed by nature, nor for what use it is.

23d. Good news beyond all expectation of the decrease of the plague, being now but 79, and the whole but 273. So home with comfort to bed. A most furious storm all night and morning.

From The Diary of Samuel Pepys. January 1666.

ABOUT THE AUTHORS
Heather Davis is a Research Associate in the Department of Pharmacology. She earned her Ph.D. in 1971 for a thesis entitled "The release of prostaglandins in vivo".
Neil Douglas is the Senior President of the Royal Medical Society.
Elizabeth Edmond is a medical graduate researching into the epidemiology of Infectious Mononucleosis in the Edinburgh student population.
Donald Gardner is a medical student at the University of Illinois.
Iain Palin is a medical student at Edinburgh University.

ANSWERS TO THERAPEUTICS PROBLEM
Yes, this question is relevant. Certain cooking oils contain methyl polysiloxane, a silicone that apparently interferes with the absorption of anticoagulants. Similar compounds are used in some preparations prescribed for hiatus hernia. (E.G. "Crisp n'Dry" and "Asilone") Reference: Talbot, J. M. & Meade, B. W. LANCET (1971) i 1293.
REVIEWS

BEHAVIOUR OF THE HUMAN URETER IN HEALTH AND DISEASE
James Ross / Peter Edmond / Ian Kirkland
Churchill-Livingstone 1972. £3.50

This excellent book, as well as recording the results of the authors' research on the pressure and wave patterns of the ureter in health and disease, presents a concise summary of contemporary thought on each topic dealt with.

The clinical side is not forgotten as each chapter has radiographs and clinical cameos of the disease process under investigation. The clinical application of the author's technique is exemplified in the chapter on the effects of drugs. It would appear that the more frequent use of atropine and morphine in renal colic is indicated.

Unfortunately the cost of this excellently written and produced book puts it beyond the reach of the average student.

Jim Loose

MEDICAL TREATMENT, A TEXTBOOK OF THERAPY IN FOUR VOLUMES
Volume VI. K. Maclean & G. Scott
J. & A. Churchill, London 1971. £2.25.

Unlike other books of this type, this paperback textbook gives an immediate source of information in a concise and readable manner.

The actual context of medical treatment has emphasis on the patient rather than disease yet there is no guarantee of success in its suggested medical treatment.

Fraser R. Lindsay

PROCEEDINGS OF THE SYMPOSIUM ON EPIDURAL ANALGESIA IN OBSTETRICS
1972, London
Editor, Andrew Doughty, M.B., B.S., F.F.A.R.C.S.
Published by H. K. Lewis & Co. Ltd. London.
Price £1.50

This book records the proceedings, of one of the bi-annual meetings of the Obstetric Anaesthetists Association, devoted entirely to discussing the various problems associated with the use of Epidural Analgesia in Obstetrics.

There is an interesting Chapter on the Anatomy and Physiology of pain in labour; many of the discrepancies in pain pathways, found by those practising Epidural Analgesia, are discussed. Maternal and foetal acid/base balance during labour and at delivery are also well covered, revealing on the whole, that, apart from introducing a possible delay in second stage of labour, Epidurals provide many benefits to both mother and baby.

The use of catcholamines, both, as locally acting vaso-constrictors, effecting the uptake and "placentation" of local analgesic solutions, and as vaso-pressers in the event of pharmacologically induced hypotension, are widely reviewed. It appears from the authors and discussants that with the advent of the newer local analgesic bupivacaine, which itself is locally-bound and therefore less readily transferred to the foetus, the use of adrenaline in the solution is only of marginal benefit and this only after frequent incremental doses and also immediately before delivery is expected. In the case of the use of vaso pressor agents it is made clear that hypotension in labour is likely to be due to (a) inferior vena caval obstruction, (b) sympathetic blockade resulting in lower limb blood sequestration, or other conditions of relative hypovolemia. Posture and expansion of the blood volume are the avenues of choice for treatment and only as a last resort should vasopressor agents be used.

There are several interesting articles devoted to technique of Epidural Block, Neurological and other complications, inferior vena caval occlusion and also the particular use of Epidurals in pre-eclampsia. The experience of one of the greatest protagonists of Epidural Analgesia is also obtained, from his observations of 1,000 cases and, finally, there is some pithy and even emotional discussion on "Why are Epidurals not more widely practiced"?

This 115 page book is a "must" for all who are interested in Analgesia in Labour. There is much science and good commonsense and little wasted reading material.

J. Wilson, F.F.A.R.C.S.
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