RES MEDICA
Journal of the Royal Medical Society

# Contents





ISSN: 2051-7580 (Online) ISSN: 0482-3206 (Print)
*Res Medica* is published by the Royal Medical Society, 5/5 Bristo Square, Edinburgh, EH8 9AL

*Res Medica,* Spring 1967, 5(3)
doi: 10.2218/resmedica.v5i3.462

V. No. 3. 295 SPRING 1967

# res
# medica

# Mind your own business

with Bank of Scotland help. You can make good use of the many B of S services which are designed to help you mind your own business—speedily and efficiently.

**FOREIGN & OVERSEAS** transactions of every kind are undertaken with any part of the world. Special study has been given to the needs of exporting companies.

**STANDING ORDERS** — The Bank will arrange to meet insurance premiums, hire purchase and other fixed payments when due, on your account.

**CREDIT TRANSFERS**—The Credit Transfer System facilitates the settlement of bills and accounts, and provides a time and money saving means of distributing salaries, wages, etc.

**COMPANY REGISTRAR**—All matters relating to company shareholdings, dividends, new issues, etc., are handled by the Registrar Department which has adopted computer procedures for the rapid processing of data.

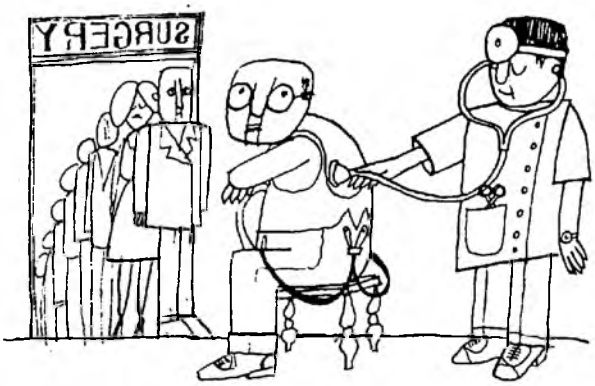
**TRAVELLING BANK** — Mobile offices attend Agricultural Shows and other events throughout Scotland.

**NIGHT SAFES** are installed at many Branches for lodgment of money outwith banking hours.

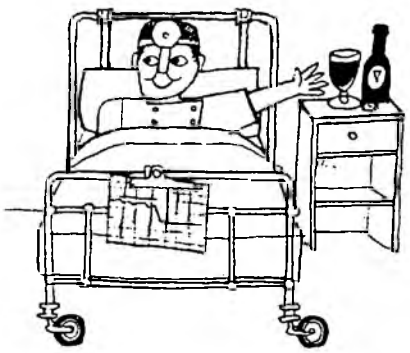
**We will gladly give you more details of these and other Business Services available from over 400 Branches throughout Scotland.**

# BANK OF SCOTLAND

## You're better with the B of S




**G**.P.'s life unending struggle;
**U**nder bedclothes just as snuggle,
**I**diot woman on the phone,
**N**itwit child ate cortisone:
**N**ot surprising he feel cynic,
**E**ndless queue at morning clinic,
**S**imply saying feel tired out!
**S**o does doctor. Have some stout.



# Res Medica

## The Journal of The Royal Medical Society

VOL. V. NO. 3. SPRING 1967



ONE SHILLING AND SIXPENCE

PUBLISHED TWICE YEARLY BY THE ROYAL MEDICAL SOCIETY

FIVE YEAR SUBSCRIPTION — ONE POUND

**Q What are the positive benefits of ATROMID-S to patients with angina pectoris, or with biochemical evidence indicating enhanced liability to myocardial infarction?**

*A* ATROMID-S has been shown to correct or favourably affect all the blood lipid (cholesterol and triglyceride) and thrombogenic factors which are correlated with enhanced liability to myocardial infarction.

Figures from controlled trials of ATROMID-S are not available yet but it would certainly seem more than justifiable to use ATROMID-S at least selectively at this stage.

*In long-term but uncontrolled trials in patients with angina pectoris and a history of myocardial infarction, the mortality and recurrence rates are lower than those of other published series of cases.**

* *Prog. in Biochem Pharmacol 1966 (In press)*

250 mg. clofibrate in red soft capsules

The usual dosage is 2 or 3 capsules after food (average 8 capsules daily)

**Atromid-S**

Clofibrate

TRADE MARK

THE QUEEN'S AWARD TO INDUSTRY 1966

*A product of original ICI research*

ICI

Imperial Chemical Industries Limited Pharmaceuticals Division
Alderley Park Macclesfield Cheshire

Ph 515/3m

# CONTENTS

# JOURNAL

*of the*

ROYAL COLLEGE

*of*

SURGEONS

*of*

EDINBURGH

*Published Quarterly:* October, January, April, July

*Annual Subscription: 21s. post free*

**Editor: Sir JOHN BRUCE**

C.B.E., T.D., Hon. D.Sc., F.R.C.S. Ed., Hon. F.A.C.S., Hon. F.R.C.S. Eng., Hon. F.R.C.S.I., Hon. F.R.C.S.G., Hon. F.C.P.S.G.(S. Afr.), Hon. F.R.A.C.S.

# EDITORIAL

Above all it demands public opinion. The population explosion, if not so much a question of space lack as of grotesque insufficiency, must be cured by those who prompted it. We demand quality not quantity of human life; alas the antibiotic era and public health propagation have brought them both.

Of course contraception brings problems. Ethically it is more acceptable to provide for every life born than to put a brake on conception and birth. But when time is running out and inefficiency proves as much a part of life as love, this philosophy becomes repugnant. We have tampered with death in a big way; it is no different to have birth control.

This is old hat. Yet world opinion (this is where the medical man comes in) must side supportively for planned contraception. Mercifully the stage is past when differentially coloured "safe period" beads were sent out to Asians, many of whom were colour blind from malnutrition. Intrauterine devices hold out much hope, and scope. Even the sacred cows of India may be suitably fitted, so great has been their increase in numbers.

A large family satisfies an otherwise unresolved for creativity in poverty-stricken parents. This provides a real socio-psychological problem. So does the fear in some men that virility is in doubt where offspring are scanty on the ground. What is forgotten is that in regions where populations may be decimated by famines or epidemics there is a significant natural tendency for the birth rate to rise. This takes a generation or two to subside when environmental parameters modify. And another fact for sober consideration: Britain's population is almost 55 millions; by 1980 it may be 65 millions. To be truly self supporting on the world food market our population would have to be in the region of 40 millions. We are contributing to world hunger in no uncertain measure.

---

The Society's much-trumpeted change in environment has brought with it a healthy change in attitude and in image. Release from the stigma of sexual apartheid and similar anachronisms has dispelled for ever the "magic circle" image of the Society. In its place has grown a Society modern, vigorous and above all more palatable to the average medical student.

Appropriately at this time comes a new look for this the Society's Journal. Cover and format have been redesigned and content has been expanded to include extracts from private business such as case presentations and accounts of undergraduate research done in this medical school.

These and other changes in the Journal have been made possible by the constant advice and encouragement of Sir John Bruce and the assistant editor of the College of Surgeons Journal, Miss Hannah Harkins, to whom our grateful thanks are due.

# NEUROLOGICAL EXAMINATION

**J. B. STANTON, F.R.C.P.E., F.R.C.P., D.P.M.**

*Neurological Unit, Northern General Hospital.*

**THE SECOND OF TWO ARTICLES WRITTEN FOR RES MEDICA**

The first of these two articles dealt with the examination of the cranial nerves, and the present article is concerned with the examination of the remainder of the nervous system. This comprises the examination of the limbs and trunk, and three main aspects have to be considered : (1) the motor functions,
(2) the sensory functions, and
(3) the reflexes.

It is usual to proceed by testing all three aspects first in the uppere limbs, then on the trunk, and finally on the lower limbs, but there can be no objection to testing first the motor functions of all regions of the body, followed by the sensory functions and then the reflexes, if the student finds this approach easier.

## *MOTOR FUNCTIONS IN LIMBS AND TRUNK*

The first approach should always be by inspection. This will reveal any wasting of muscles, any involuntary movements, or any abnormal posture of the limbs, and will also enable any trophic changes to be observed. Wasting is a feature of lower motor neurone damage and may be accompanied by fasciculation, that is to say the twitching of groups of muscle fibres comprising an individual motor unit. Fasciculation may occur when there is incipient damage or degeneration of the anterior horn cell and the proximal part of the axone. Involuntary movements which, as the name suggests, are not under the control of the patient, may be of various types, the commonest being tremor. This may be the result of extra-pyramidal disease such as Parkinsonism or may be an exaggeration of physiological tremor as in anxiety neurosis, and thyrotoxicosis and other toxic states. The movements of chorea, which are semi-purposive, and the repetitive writhing movements of athetosis may also be seen, either combined (choreo-athetosis) or in pure culture. Abnormalities of posture of the limbs may reveal underlying disease of bone or joints or contractures of disused muscles, but they may also be characteristic of damage to various parts of the nervous system, as when the increased activity of the anti-gravity muscles produces the typical flexed posture of the upper limb in hemiplegia. After inspection the examination of the motor functions proceeds with the assessment of tone, power, co-ordination and maintenance of posture, and gait and these aspects will now be considered in turn.

### ASSESSMENT OF TONE

This can only be achieved with considerable experience since it depends on two variables : (1) the patient's ability to relax, and (2) the observer's ability to assess objectively the degree of resistance offered to his movements of the patient's limbs. Usually tone is assessed in the limb muscles by passive movements of the wrist, elbow and shoulder, ankle, knee and hip. In addition in the lower limbs clonus may be tested for, at the knee by

extending the joint and pushing the patella sharply towards the anterior tibial tubercle, and at the ankle by forcibly dorsiflexing the foot. The repetitive contraction and relaxation of the muscles which constitutes clonus is usually the sign of an upper motor neurone lesion. Tone may be pathologically increased, as in spasticity due to an upper motor neurone lesion or in rigidity due to an extrapyramidal lesion. Spasticity is recognised by its "clasp-knife" character which describes the manner in which resistance to passive stretching of the muscle by moving a joint is maximum during the first part of the attempted movement and then breaks down suddenly, like the opening of a pen-knife blade. In contrast rigidity causes a uniform degree of resistance to muscle stretching throughout the range of movement of the joint. Tone may also be pathologically decreased, as in the hypotonia of a lower motor neurone lesion or of cerebellar hemisphere lesions.

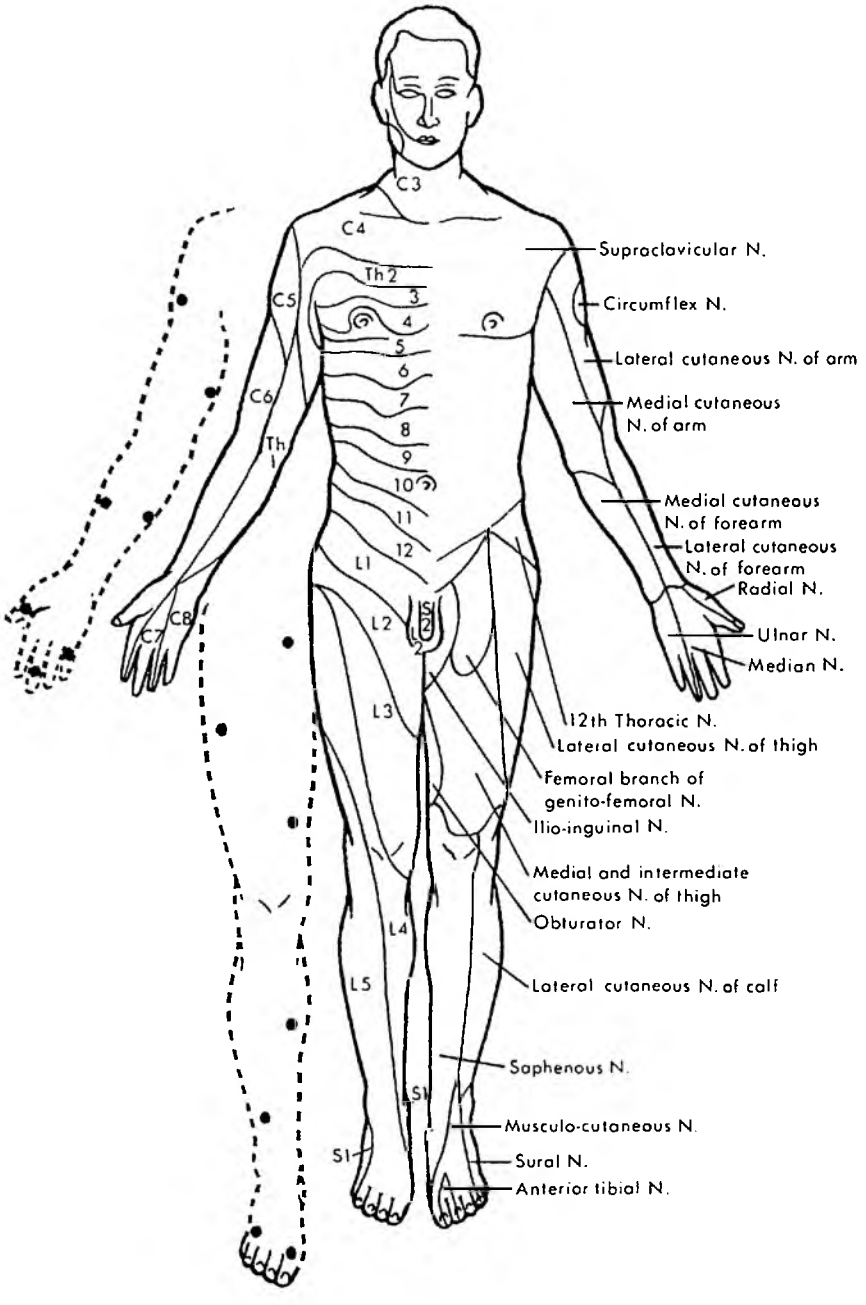
#### POWER

Muscular weakness is one of the cardinal signs of neurological disease and may result from disease of the muscle itself, as in myopathy, or from disease of the motor nerve, as in peripheral nerve and limb plexus lesions, or from disease of the anterior horn cell in the grey matter of the spinal cord. Weakness of voluntary movement will also result from interruption of the pathways (pyramidal tracts) between the motor cortex and the anterior horn cells or motor cranial nerve nuclei. Paralysis may also of course be a symptom of hysteria. When testing a patient's power it is usual to estimate the force which the patient can apply in performing a movement requested by the examiner. For instance the patient may be asked to flex his elbow while the examiner, grasping his wrist, tries to prevent the movement. Routinely, power in the upper limb is tested by assessing the strength of the hand grip, of dorsiflexion and plantar flexion of the wrist, of flexion and extension of the elbow, and of abduction and adduction at the shoulder. In the lower limb, dorsiflextion and plantar flexion of the foot, flexion and extension of the knee, and flexion, abduction and adduction of the hip are tested. If any weakness is found during the course of this routine survey then the power of individual muscles will have to be assessed in the light of the knowledge of their anatomical actions. When there is some doubt as to whether the patient is exerting full power in performing the movements asked of him, it is sometimes useful to change the procedure and ask the patient to keep the joint fixed in a certain position while the examiner attempts to move it. If in this situation the strength of the muscle appears to be good, whereas in voluntary movement it appears poor, then this may well be due to lack of co-operation by the patient or to hysteria rather than to true organic weakness.

#### CO-ORDINATION AND MAINTENANCE OF POSTURE

Co-ordination may be impaired by muscular weakness alone, but when it is disturbed in the absence of such weakness it is usually the result of damage to the cerebellar mechanisms (*i.e.* to the spino-cerebellar pathways, to the cerebellum itself, or to its connections with the motor cortex and basal ganglia), or to loss of proprioceptive sensation from muscles, joints and tendons. This latter form of incoordination is usually known as sensory ataxia and the former as cerebellar ataxia. Disturbance of co-ordination is often associated with an inability to hold the limbs in a steady posture. In the first place therefore the patient should be asked to stretch out his arms and to keep them steady in front of him. A similar test in the lower limbs is carried out on each side in turn by asking the patient to hold the leg at an angle of 45 degrees to the horizontal while lying on his back. In a patient with cerebellar disease, the limb on the side corresponding to the cerebellar lesion will often be found to waver whether the eyes are open or shut. On the other hand the patient with sensory ataxia will be able to maintain the posture of his limbs normally with the eyes open, but when he closes his eyes the posture of the affected limb will become unstable. This is because the visual sense can compensate to a considerable degree for loss of proprioceptive information from a limb. Co-ordination is also tested in the upper limb by the finger/nose test in which the patient is asked to place the tip of his index finger on the tip of his nose. This again should be performed first with the eyes open and then with the eyes closed to distinguish between cerebellar and sensory ataxia (see above). The corresponding test in the lower limb is the heel/knee test in which the patient, lying supine, is asked to place the heel of one foot on the knee of the other leg and to run it

Fig. 1




By courtesy of Messrs E. & S. Livingstone Ltd.

steadily down the front of the shin bone. In either of these tests inco-ordination is revealed by oscillation of the moving limb in place of the normal smooth, steady movement. In particular an oscillation seen mainly at the end of the action, when the target (nose or knee) has almost been reached, is called intention tremor and is a sign of cerebellar ataxia. Rapid alternating movements are also impaired by inco-ordination and can be tested by asking the patient rapidly to pronate and supinate the forearms or, while lying on his back, to tap with the heel of one foot on the middle of the opposite shin.

#### GAIT

The examination of the gait and stance is an important part of testing the motor functions. The patient is asked to walk up and down and any abnormality is noted. Abnormalities may be the result of unilateral disability, as for instance in the gait of hemiplegia, or of bilateral disability, as in the slow stiff gait of a patient with spastic paraplegia. The disturbance may be less one of spasticity and weakness that of ataxia in which case the patient will walk with a broad wide-based gait, his feet held wide apart in an attempt better to maintain his balance. The short shuffling steps of Parkinsonism, and the loud slapping of the foot on the ground in a patient with paralytic footdrop, are characteristic disturbances which may be recognised. After his gait has been observed the patient should be asked to stand with his feet together and to maintain his balance which he should normally be able to do. He is then asked to close his eyes and should still be able to maintain his balance, unless he has a sensory ataxia of the lower limbs in which case he will sway or fall. This is Romberg's test.

#### THE REFLEXES

Routine examination of the nervour system includes the eliciting of the tendon reflexes of the jaw and limbs, and the abdominal and plantar responses.

The tendon reflexes are stretch reflexes and are elicited by a sudden stretch of the muscle usually brought about by striking the appropriate tendon with a sharp blow from a tendon hammer. The tendon reflexes are diminished or abolished by any lesion which interrupts the segmental reflex arc, and they are enhanced when damage to the cortico-spinal pathways releases the segmental reflex arc from inhibitory influences from higher levels of the nervous system.

The secret of eliciting the tendon reflexes efficiently is to place the relevant part of the body in the correct position. This should be such as to ensure that the length of the muscle involved is roughly midway between full shortening and full lengthening. The jaw jerk is elicited by grasping the patient's chin between the forefinger below and the thumb above. The patient is instructed to relax and to allow his jaw to hang half-open and the examiner's thumb is then struck a glancing blow with the tendon hammer, thus causing a sudden stretch of the masseter and temporalis muscles which gives rise to a reflex contraction. The jaw jerk is normally rather sluggish, but is clearly exaggerated in the presence of a bilateral upper motor neurone lesion above the level of the motor nuclei of the trigeminal nerves in the pons. In the upper limbs, the biceps jerk (segmental level C5, 6) and the brachioradialis or supinator jerk (C5, 6) are both tested with the patient lying supine and the arms slightly abducted at the shoulder with the hands resting on the abdomen while the elbows are half-flexed. The examiner's thumb or finger is placed firmly on the tendon of the biceps muscle immediately above the cubital fossa and is struck with the hammer. The supinator jerk is produced by striking the head of the radius at the wrist. To elicit the triceps jerk (C6, 7), the forearm of each side in turn is pulled across the patient's chest and the triceps tendon struck directly above the olecranon process. It is convenient to compare the reflexes of the two sides directly by eliciting each reflex first on one side and then on the other. In the lower limbs, the knee (L2, 3, 4) and ankle jerks (L5, S1) are tested. With the patient lying flat on his back the knees and hips are semi-flexed and the examiner passes his arm below the knees to support their weight and allow the patient to relax. The patella tendon is then struck on each side in turn. To elicit the ankle jerk, the hip is abducted and externally rotated with the knee flexed. The foot is dorsiflexed by the examiner's hand pushing against the ball of the foot, while he strikes the Achilles tendon with the hammer. The abdominal responses (D8-12) are tested by slowly and *lightly* stroking the abdomen with a pin. The stroke should be towards the mid-

line, parallel to the costal margin for the upper quadrants and parallel to the inguinal ligament for the lower quadrants. The abdominal responses disappear in the presence of an upper motor neurone lesion. The plantar response ($L_5$, $S_1$, 2) is elicited by scratching the sole of the foot with a pointed (but not sharpened) object, such as the end of a Yale key. The stimulus should be applied to the outer border of the sole, commencing near the heel and passing forwards to the base of the 5th toe and then turning medially across the ball of the foot towards the base of the great toe. This stimulus will produce reflex flexion of the great toe in normal persons, but in the presence of a lesion of the pyramidal tract the great toe will dorsiflex instead.

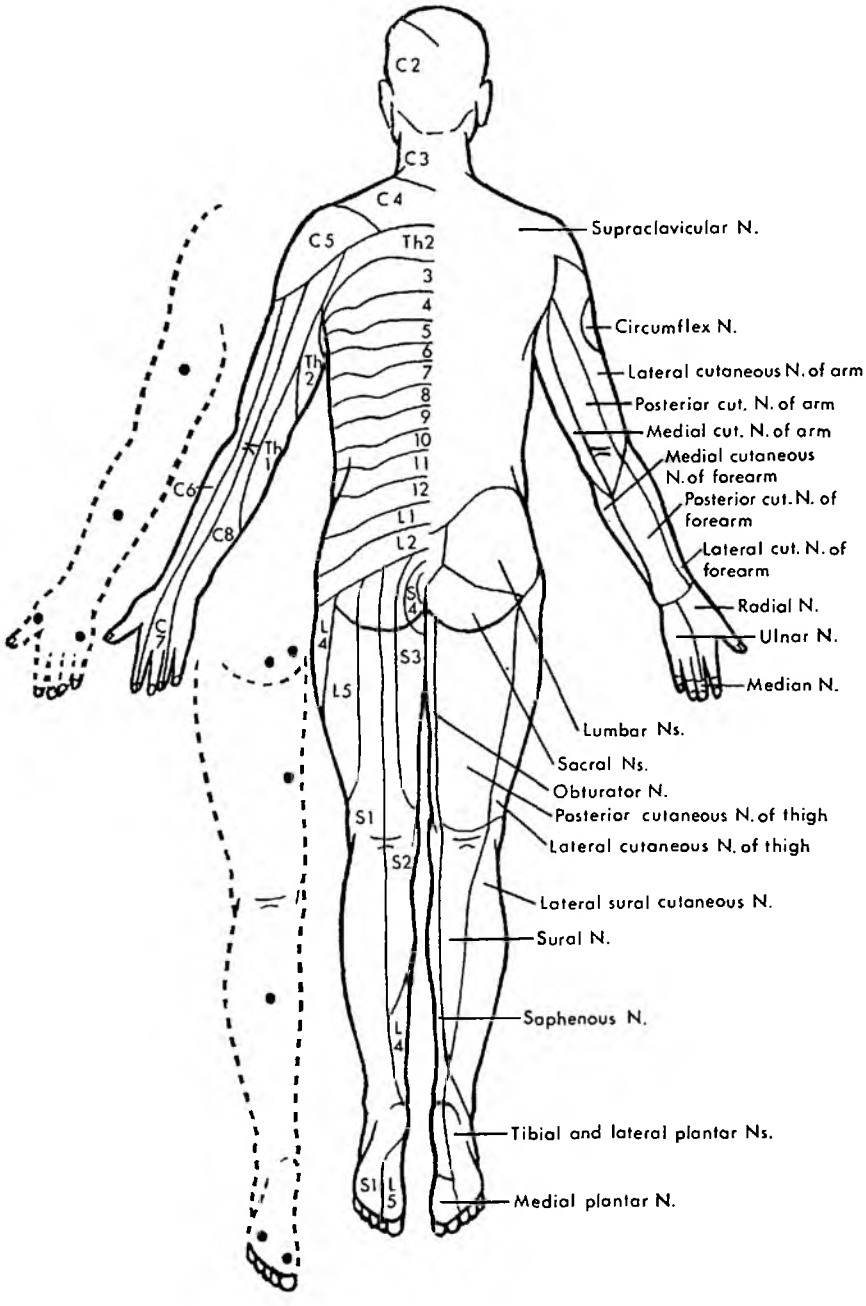
## *SENSORY FUNCTIONS*

Sensory testing may be a fatiguing exercise both to the patient and for the examiner. If the patient is not in a clear mental state or if he becomes tired during the course of the examination then his answers will become inconsistent and worthless.

A number of different modalities or forms of sensation must be tested over the whole of the surface of the body during the examination. The different modalities of sensation include pain, temperature, light touch, vibration sense, and the sense of passive movement, and the student is less likely to omit testing one of these modalities if he adopts a systematic routine of his examination. It is helpful to remember that pain and temperature sensation travel together in the spino-thalmic tract of the spinal cord, and that light touch, vibration sense and proprioception travel in the dorsal columns. With this in mind it is logical to test the two spino-thalmic modalities, pain and temperature, one after another and then to continue with the modalities carried through the dorsal columns. Alternatively one may test superficial (cutaneous) sensation — pain, temperature and light touch — in one group, and deep sensation, including vibration sense and sense of passive movement, in another. Pain sensation is tested with a pinprick, temperature sensation with tubes filled with hot or cold water, and light touch with cotton wool. Vibration sense is tested by applying a tuning fork vibrating at 256 cycles per second to various bony prominences. Sense of passive movement is tested by moving the terminal phalanx of a digit in the hand or foot up or down and asking the patient to indicate the direction of movement while his eyes are closed. When there is no reason to suspect from the history that the patient has loss of cutaneous sensation, a fairly rapid survey of the limbs and trunk will serve to determine whether sensation is intact. Should an area of apparently altered sensation be found however, then it will be necessary to examine it more closely and to delimit its extent and outline. Cutaneous sensation may be impaired by lesions at any point between the sensory nerve endings in the skin and the sensory cortex, and the area and distribution of sensory loss on the skin will depend on the site of this lesion. Figures 1 and 2 indicate the peripheral nerve supply and segmental or dermatomal distributions on the skin of the trunk and limbs. By applying the stimuli for temperature, pain and touch to the points indicated by the black dots in the haloes to these figures, it will be seen that a fairly rapid assessment can be made of the integrity of sensation in both peripheral nerve and dermatomal territories of the limbs. Sensation on the front and back of the trunk should be tested from below upwards on each side of the midline. The most satisfactory procedure is to determine in the first place the integrity of cutaneous sensation all over the body. This should be done as quickly as possible so as not to fatigue the patient. If an area of apparent alteration of sensation is found the examiner should finish checking the sensation in other parts of the body before returning to a more detailed examination of the abnormal area. It may be wise to carry out this more detailed examination on another occasion, if the patient has become fatigued. When plotting the boundaries of such an area one should move the stimulus from the region of lessened sensitivity towards that of normal sensitivity, since the transition to normal sensation is most easily appreciated by the patient. It is noteworthy that when vibration sense and position sense are impaired they are almost invariably lost initially from the periphery, and for this reason if they are found to be intact at the distal phalanges then there is no need to test them more proximally.

*Cortical sensory functions.* Lesions of the sensory cortex in the post-central gyrus do not usually cause marked loss of sensation in the corresponding parts of the opposite side of the body, but impair the discriminative faculties in that part. For instance there may be inability to distinguish by palpation alone be-

Fig. 2




By courtesy of Messrs E. & S. Livingstone Ltd.

tween the different shapes of objects held in the hand, or to discriminate between different textures, weights, etc. These discriminative functions are a property of the cortex, which extracts the necessary information from the basic sensory modalites and there are no separate 'discriminative' pathways. The integrity of the cortical sensory functions can only be tested profitably therefore if it has been shown that there is no impairment of sensation from interruption of the sensory pathways in the peripheral nerves, or in the spinal cord and brainstem. There are three simple tests of cortical sensory function : tactile localisation, two-point discrimination, and stereognosis. In testing tactile localisation the patient is asked to close his eyes and he is then lightly touched with a blunt object and asked to indicate the point on the body so touched. Two-point discrimination is the ability to distinguish between two separate points when applied close together. This can be tested by applying two pinheads simultaneously or with the aid of a specially designed pair of compasses. The threshold at which two points can be discriminated from one another on the pulp of the finger is less than 5 mm. in the normal. On the foot it is considerably greater and is about 3 cms. on the sole of the foot. Stereognosis implies the ability to recognise objects by palpation without looking at them. The patient is asked to close his eyes and various small objects, such as coins of different denominations, a safety pin, or a key, are placed in his hand and he is asked to identify them by palpation alone. Each hand is tested separately for accuracy in recognition.

*Other higher cortical functions.* In addition to cortical sensory functions, the functions of language, the ability to perform complicated voluntary movements, and the ability to recognise objects by sight or hearing may be tested. Impairment of these functions is called aphasia, apraxia or agnosia respectively. These and the intellectual functions in general are not tested routinely, but only in cases where cerebral damage is inferred and for the sake of brevity they are not considered in detail in this article. At this point however it may be emphasised again that the examination of the nervous system is only one part of the general medical examination and that a full medical examination must be carried out in each neurological patient.

## *INTERPRETATION OF THE PHYSICAL SIGNS*

Reference has already been made in the first of these two articles to the importance of taking a full clinical history in neurological disorders, as in any other branch of medicine. The physical examination usually enables the physician to diagnose the site of the lesion in the nervous system — the "anatomical diagnosis". The final or "aetiological diagnosis" is arrived at by relating this anatomical diagnosis to the information contained in the history, which may indicate the nature of the pathological process which is at work, e.g. congenital, infective, traumatic, neoplastic, vascular, degenerative, etc. Often however it may be necessary to resort to further sources of information such as X-rays, examination of the cerebrospinal fluid, electroencephalography, cerebral angiography, etc., before a final diagnosis can be reached.

By eliciting the physical signs described in these two articles, the student will be able to reveal the defects in the patient's performance and, from his knowledge of the anatomy and physiology of the nervous system, he should then be able to determine at which point the nervous connections have been interrupted. For instance, the patient may have an impairment of his motor functions, whether in the motor cranial nerves, the limbs or the trunk. This may take the form of weakness, indicating either an upper or lower motor neurone lesion or primary muscle disorder. It may take the form of alteration of tone, such as the spasticity of an upper motor neurone lesion or the rigidity of basal ganglion disease, or it may take the form of ataxia and inco-ordination, indicating disease of the cerebellar or proprioceptive pathways. Various combinations of signs of motor dysfunction may indicate which pathways or groups of nerve cells are damaged. A combination of wasting, fasciculation, weakness and decreased tone in the muscles, together with loss of the corresponding tendon reflexes, are the signs of a *lower motor neurone lesion*, indicating damage somewhere between the anterior horn cell and the affected muscles. In contrast, weakness without wasting, but with increase of tone, exaggeration of tendon reflexes, absent abdominal repsonses, and an extensor plantar response on that side of the body, all indicate an *upper motor neurone lesion*. When the sensory functions are impaired, there may be

involvement of the special senses of smell, taste, vision and hearing, or of cutaneous and/or deep sensation. The impairment of both cutaneous and deep sensation in a relatively small area of the skin surface will suggest a peripheral sensory nerve lesion. The selective impairment of pain and temperature sensation with preservation of light touch, joint sense and vibration sense, indicates that the lesion exclusively involves the spino-thalamic tract. Conversely the dorsal columns may be involved alone, in which case light touch, joint position sense and vibration sense are impaired. Such selective disturbances can arise only from a lesion situated in a part of the nervous system where the spino-thalamic tracts and the dorsal column pathways are sufficiently separated in space for one to be involved without the other, i.e. in the spinal cord or lower brain stem. The finding of a "sensory level" on the trunk above which sensation is normal may reveal clearly in which segment of the spinal cord the lesion lies. Sometimes the anatomical diagnosis will not indicate a discrete lesion of a relatively small area of the nervous system, but will show that various widely separated cell groups and fibre pathways which nevertheless have close functional connections, are diffusely and selectively involved. For instance there may be evidence of combined upper motor neurone and lower motor neurone damage without any signs of sensory or other impairment. This situation occurs in amyotrophic lateral sclerosis, a form of motor neurone disease arising from widespread degeneration of the upper motor neurones (the Betz cells in the motor cortex), and of the lower motor neurones situated in the motor cranial nerve nuclei and in the anterior horns of the spinal cord.

From what has been said earlier it will be realised that the routine neurological examination which has been described in these two articles is the *minimum* which should be carried out and that the finding of abnormal signs will lead to more detailed attention being paid to the functions found to be impaired. With practice it is possible, while carrying out the examination to keep constantly in mind the various possible sites of damage in the nervous system that are suggested by the physical signs being elicited, and then to look for further signs which will confirm or refute these possibilities. In this way the clinical examination of the nervous system develops into a truly logical investigative procedure.

# SOME ASPECTS OF CIRCULATORY STABILITY

N. C. H. STOTT, B.Sc., M.B.Ch.B.

Based on a dissertation read before the Society on 11th February, 1966.

The secrets of the circulatory system taxed the imaginations and resources of workers in every field of medicine long before even William Harvey produced his classical treatise in 1628. Now, in 1966, the basic anatomy of the circulatory system is widely accepted but the relative importance of various homeostatic mechanisms in the patho-physiology of this system is still the subject of constant debate; this is no mere 'academic exercise', for the disorders of the circulatory system are becoming major problems throughout the world and they merit careful consideration. Nevertheless this dissertation is not a review. I attempt to outline a few aspects of the subject which are of particular interest, and so well accepted and established concepts are included along with some more recent work.

One of the most remarkable facts about the human body is the day to day stability of its total weight (Robinson and Watson, 1965). This stability implies a relative stability of our fluid volume, and especially our extra-cellular fluid volume which bears a fairly constant relationship to total body weight in normal man (Moore, 1965). A patient's weight is therefore a sensitive indicator of his fluid balance and, to the clinician, it usually reflects the state of his extra-cellular fluid.

The extra-cellular fluid is normally an isotonic solution with an osmolality of 283±11m. osmols/litre in which the principal ions are sodium, chloride and bicarbonate. The transcapillary exchange of this fluid is governed by the balance of differential hydrostatic pressure, colloid osmotic pressure, tissue pressure and capillary permeability, so an adequate extracellular fluid volume is fundamental to the maintenance of a circulating blood volume.

## OSMO-REGULATION AND VOLUME REGULATION

The mechanism of osmolar regulation of the extra-cellular fluid is better understood than volume regulation and it is a process students are familar with. Osmo-receptors somewhere in the distribution of the internal carotids are sensitive to a 2% change in osmolality (Pitts, 1964). Afferent neural impulses are co-ordinated centrally and anti-diuretic hormone is released by the neuro-secretory mechanism of the hypothalamo-hypophysial system. The kidney is the effector organ and excretion of free water is varied by the action of anti-diuretic hormone on the distal tubules and collecting ducts. Thus in this system we have recognised a stimulus, a receptor, a central controlling mechanism, a humoral effector agent and the effector organ. The details need not concern us but it is worth remembering that thirst is part of the osmolarity controlling complex. Haemorrhage, emotion, tobacco, alcohol and many other factors can also influence anti-diuretic hormone output.

The osmolarity of the body is controlled very largely by alteration of intake and excretion of water, but sodium is the predominant ion in the extra-cellular fluid and the following three experiments illustrate how its homeostasis can influence osmolarity and volume regulation in the body:—

1. *Hypertonic saline* injected into the carotid artery induces an acute thirst and anti-diuresis associated with anti-diuretic hormone output (Best and Taylor, 1961). Here, in the interests of maintaining normal osmolarity, the body retains water to dilute the saline and thereby increases its extra-

cellular fluid volume. Re-establishment of normal extra-cellular fluid volume is achieved by subsequent excretion of the excessive salt and water. Thus volume regulation of body fluids is an integral part of the regulation of sodium excretion and clearly a derangement of this system will cause oedema or dehydration.

2. *Salt excess.* Normal man can cope with about 10 grams of salt per day in his diet, as any excess is excreted in the urine, but man is relatively intolerant of high salt intake; 30-40 grams of salt per day causes an elevation of body weight of 5-15lbs. above normal. This weight increase is due to extra-cellular fluid expansion, and if the high sodium intake is maintained, the body weight stabilizes at this level, the kidneys just managing to excrete the excessive intake when the extra-cellular fluid volume has expanded a little (vide infra). Thus, even with normally functioning kidneys, man has been described by Pitts (1959) to be, 'but a salt-shaker away from incipient oedema'.

3. *Salt depletion.* Normal young men on salt free diets, but encouraged to drink plenty of water, undergo progressive weight loss for 4-5 days and remain in negative salt and water balance, indicating an isotonic contraction of their extra-cellular fluid. During the subsequent week the subjects stop excreting salt and start retaining water. Their weight stops falling so rapidly and during the latter phase water is retained despite increasing hypo-osmolality of the extra-cellular fluid. An explanation is that initially osmo-regulation dominates, causing an isotonic contraction of the extra-cellular fluid, but latterly the volume of fluid in the body is so depleted that another mechanism dominates, to cause water retention, despite the extra-cellular fluid dilution. Anti-diuretic hormone is probably the mediator hormone but it appears that osmo-regulation is sacrificed in this circulatory emergency and volume regulation dominates. (McCance, quoted by Borst et al, 1961).

Two points from these experiments should be emphasised. a) Men may vary in their ability to excrete a chronic salt load but in general this is limited to a few grams more than the average daily intake. b) The volume control mechanism seems to be an extremely powerful one — teleologically one could suggest that this is necessary to maintain vital circulation of blood in the face of osmolar and metabolic derangements.

These experiments each represent a considerable challenge to the internal milieu of the body and it may be argued that this detracts from their value as physiological experimental models. Nevertheless it is recognised that any procedure which causes a minor reduction in the effective blood volume also causes salt and water retention, and vice versa. Thigh tourniquets to exclude venous return from the legs, a change in posture from recumbency to standing, an acute haemorrhage or the sudden opening of an arterio-venous fistula all induce salt and water retention. On the other hand, release of the tourniquet, assumption of recumbancy, infusion of plasma expanders or closure of the arterio-venous fistula each induce a measurable salt and water diuresis in normal man (Pitts, 1959; 1964). In each of these instances the water diuresis and anti-diuresis is determined by anti-diuretic hormone. This can be demonstrated by blocking anti-diuretic hormone release with alcohol, e.g. when thigh tourniquets are applied the usual anti-diuresis is diminished by the absence of anti-diuretic hormone, but the natriuresis persists (Borst et al, 1961). It is believed that volume (stretch) receptors in the thorax send afferent impulses via the vagus to initiate anti-diuretic hormone release during volume depletion. This reflex has been established in animals by abolishing it after vagal section or freezing (Welt, 1964), and it is possible that the vagal afferents stem from stretch receptors in the left atrium (Pitts, 1964).

#### SODIUM HOMEOSTASIS

The mechanisms of salt retention are poorly understood. Aldosterone from the zona glomerulosa of the adrenal cortex causes sodium retention, and in recent years it has been shown that renin, through its conversion product angiotensin, stimulates the secretion of aldosterone (Bartter et al, 1961). There is good evidence for increased serum levels of aldosterone in many salt retaining states, e.g. haemorrhage, congestive cardiac failure, cirrhosis, thigh tourniquets (Borst et al, 1961) and prolonged standing (Mills et al, 1960; Gowenlock et al, 1959). However the natriuresis of recumbency or released tourniquets is not prevented by exogenous aldosterone and spironolactone (an aldosterone antagonist) does not block the anti-natriuresis of standing or application of tourniquets (Gowenlock et al, 1969; Mills et al,

1960). Also adrenalectomised or Addisonian patients on steroid maintenance, in whom increased aldosterone output is impossible, have normal responses to these stimuli (Borst et al, 1961; Pitts, 1964). Furthermore, aldosterone has a latent period of about 40 minutes before it is physiologically active (Pitts, 1964), whereas the salt retention which follows acute volume depletion is immediate. These findings suggest that acute salt retention is mediated by some mechanism other than aldosterone and the renin-angiotensin system.

Recently Brown et al (1965-66) have produced more evidence for the view that changes in sodium balance are the cause rather than the result of variations in renin output. These workers reached this conclusion after assaying the plasma renin and electrolytes in a series of 253 hypertensive patients, in whom they demonstrate an inverse relationship between plasma renin and plasma sodium. However, the sodium ion does not necessarily affect the juxta-glomerular apparatus directly because body sodium may exert its influence by affecting the blood volume, renal plasma flow, filling of the arterial system or some other circulatory parameter; and some workers do believe that haemodynamic factors mediate the more acute changes in sodium excretion, whereas the overall day to day balance of sodium intake and output is determined by aldosterone (Pitts, 1964).

#### HAEMODYNAMIC FACTORS

A reduced cardiac output and renal plasma flow are usually associated with sodium retention (Thompson & Pitts, 1952). Therefore the hypovolaemia of salt depletion will, by Starling's Law (Pickering, 1960), induce a reduced cardiac output and sodium retention. The mechanism of this salt retention has been the source of some controversy, but Selkurt (1949; 1951) has dissociated glomerular filtration rate from sodium excretion and demonstrated that the haemodynamic factor which correlates best with sodium excretion is the pressure in the renal arterial system. Moreover it has been observed that increased tone in the afferent arterioles of the kidney induces sodium retention, whilst elevation of blood pressure without alteration of arteriolar tone produces a rapid natriuresis. It is likely that a pressure-receptor site in the kidney exists downstream from the afferent resistance but upstream from the efferent resistance (De Bono and Mills, 1965), and there is a little evidence for a locally acting humoral mediator which causes the rapid variation of sodium reabsorption (De Bono and Mills) in response to pressure changes at this site. This theoretical pressure-receptor site is remarkably near the juxta-glomerular apparatus but it remains to be seen whether this organelle is the receptor involved in these haemodynamic changes.

If this hypothesis is correct, factors which alter pressure at the receptor site should alter sodium output profoundly. Two such factors are afferent arteriolar tone, and the blood pressure. A great reduction of arteriolar tone occurs clinically in an iatrogenic postural hypotension because, on standing up, no vascular reflexes are functioning to maintain the peripheral resistance, and cardiac output also diminishes due to a reduced venous return from peripheral pooling of blood; under these conditions sodium and water retention occurs. Return to the supine position is associated with a salt and water diuresis, which is probably due to improved cardiac output and exposure of the pressure sensitive area in the kidney to higher arterial pressure (De Bono and Mills, 1965). It is unlikely that these phenomena are initiated by pressure changes in the venous system as, in attacks of paroxymal tachycardia, a sudden rise of arterial pressure is always associated with a diuresis of salt and water despite reduced central venous pressure, whilst high venous pressure in patients with congestive cardiac failure is associated with salt retention.

In a normal subject, movement from recumbancy to standing results in sympathetic reflexes which prevent a fall in blood pressure and cardiac output by increasing peripheral resistance (Wang et al, 1960). However, despite the constant blood pressure, a reduction in the excretion of sodium and water occurs when we assume an upright posture, because the increased arteriolar tone induces the kidney to retain sodium and water. This expands the extracellular fluid and permits some relaxation of arteriolar tone. A more perfect co-ordination of rapid acting and slow acting homeostatic mechanisms can hardly be conceived (Borst and Borst-de-Geus, 1963).

The concept helps to explain many unexpected phenomena in medical science, e.g. angiotensin, which has a controlling influence on aldosterone secretion, is known to cause salt retention if administered in small doses but in large doses it has a powerful pressor effect and it causes a natriuresis. Ames et al (1965) have explained this paradoxical situ-

ation by pointing out that even small doses of angiotensin, which have no pressor effect, result in a natriuresis if given for a long time. The initial salt retention expands the extra-cellular fluid, improves the cardiac output and increases the vascular reactivity to pressor agents. This exposes the kidney to pressures which are high enough to precipitate a natriuresis. These workers believe that a large initial dose of angiotensin has a pressor effect large enough to overcome the salt retaining action of the drug, by exposing the receptors to higher arterial pressures immediately.

#### CLINICAL APPLICATIONS

In congestive cardiac failure the poor cardiac output results in reduced pressure at the theoretical receptor site in the kidneys. This occurs either as a direct result of failing cardiac output or as a result of protecting afferent arteriolar spasm which occurs reflexly when systemic blood pressure falls. Salt and water retention results, and the extra-cellular fluid volume increases venous return to a heart which cannot respond by improving its performance. The patient in cardiac failure is thus conserving salt and water in an attempt to increase the plasma volume and thereby obey Starling's law. In this situation the therapeutic measure of greatest value is improvement of cardiac output and hence the diuretic effect of digitalis in many of these patients.

Essential hypertension is another problem which may prove to be a disorder of homeostasis if the concepts described above are correct (Borst & Borst-de-Gues). It is an intermittent disease in its early stages, the blood pressure fluctuating between normal and hypertensive levels, due to alteration of peripheral resistance and not cardiac output (Brod et al, 1959). There is a tendency for the blood volume of these patients to undergo greater than normal fluctuations initially (Jones et al, 1964), but in established hypertensive disease the cardiac output and extra-cellular fluid volumes are believed to be normal (De Graeff, 1957).

Tobian (1960) has reviewed many relationships between electrolyte disturbances and the development of hypertension, and the evidence is strongly suggestive of a direct association between disturbances of sodium and/or potassium homeostasis and hypertensive disease. Furthermore, epidemiological evidence from cross-cultural surveys reveals that there is an almost linear relationship between salt intake and the incidence of hypertension in various population groups (Isaacson et al, 1963).

#### EXPERIMENTAL HYPERTENSION

Borst and Borst-de-Gues (1963) produced an experimental model of essential hypertension in man which is in keeping with the hypothesis outlined above. These workers gave low doses of liquorice, which has a deoxycortone like action and causes salt retention, to patients every day for three months. Initial salt and water retention expanded the extracellular fluid volume causing rapid rise in central venous pressure and cardiac output. The arterial pressure began to rise slowly and after several weeks it attained hypertensive levels. The authors attributed this slow increase to reflexes initiated by baro-receptors in an abortive attempt to drop the rising blood pressure by increasing the renal excretion of sodium. They also postulate cardiac hypertrophy in the face of continued sodium retention and greater demands on the myocardium. Eventually a salt and water diuresis commenced and after three months the extra-cellular fluid volume and central venous pressure had returned to normal, but the subject was left with high diastolic and systolic blood pressure, i.e. a state equivalent to essential hypertension. Borst and Borst-de-Geus explain the diuresis of sodium and water by suggesting that the cardiac output and blood pressure rise, until a point is reached at which the salt retaining action of liquorice is less than the natriuretic effect of a very high renal perfusion pressure. In terms of the above hypothesis this exposes the receptor site to high pressures, and excessive extra-cellular fluid is then excreted, as occurred in this experiment. The patient is left with a hypertrophied heart which is capable of greater work at the same or lower central venous pressure than a normal heart (Borst & Borst-de-Geus). It is likely that carotid baroreceptors become adapted to the higher pressure and thus sodium excretion also requires greater arterial pressures than were previously needed.

This is a thought-provoking experimental model which puts forward a possible explanation for many of the clinical and experimental features of hypertensive disease. It explains essential hypertension as a disorder of homeostasis, and if it proves to be a correcet interpretation many cases of essential hypertension should be preventable.

In conclusion I need to quote one more

experiment. Normal young men on a standardized diet have been shown to have significantly elevated extra-cellular fluid volumes and blood volumes on Saturday morning after a hard week's work. On Monday morning after a restful weekend these volumes are back to normal (Gerbrandy, quoted by Borst, 1961). Is it possible that a combination of repeatedly busy weeks and hectic weekends, in subjects with a high salt intake and a limited capacity to excrete a salt load, could place them into the first stage of essential hypertension, as illustrated in Borst's experimental model. Here a genetic factor (ability to excrete a salt load) and environmental factors (salt intake and stress) could be operating together. These questions have not been answered and it would be presumptuous of me to speculate further. However I can refer to the conjectures of two well known workers who suggest that essential hypertension *may* be an inborn error of sodium metabolism conditioned by environmental factors (Knudsen and Dahl, 1966).


**SUMMARY**

1. Aspects of salt and water metabolism have been described with particular reference to the relationship between osmo-regulation and sodium homeostasis in the body.
2. Man's limited capacity to excrete a salt load has been emphasised and its possible pathological implications discussed.
3. Some recent hypotheses and experiments in the field of circulatory stability have been described.
4. Congestive cardiac failure and essential hypertension are discussed in the light of these findings.


*REFERENCES*


Ames, R. P., Borkowski, A. J., Sicinski, A. M., & Laragh, J. H. J. Clin. Invest 1965, *44* 1171.

Bartter, F.C., Casper, A. C. T., Delea, C.S., & Slater, J. D. H. Metabolism, 1961, *10* 1006.

Best, C.H., & Taylor, N.B. The Physiological Basis of Medical Practice. William & Wilkins Co. 1961.

Borst, J. G. G., & Borst-de-Geus, A. Lancet 1963, *1*, 677.

Borst, J. G. G., De Vries, L. A., Van Leeuwen, A. M., Den Ottolander, C. J. H., & Cejka, V. In 'Water & Electrolyte Metabolism'. Ed. C. P. Stewart & T. H. Strangers, Elseview Pub. Co. 1961.

Brod, J., Fencl, V., Hejl, Z., & Jirka, J. Clin. Sci. 1959, *23* 339.

Brown, J. J., Davies, D. L., Lever, A. F., & Robertson, J. I. S. B.M.J. 1965, 2 144, & 1215.

Ibid. B.M.J. 1966, *1* 505, & 2 268.

De Bono, E., & Mills, I. H. Lancet 1965, 11, 1027.

De Graeff, J. Acta Med. Scand. 1957, *156* 337.

Gowenlock, A. H., Mills, J. N., & Thomas, S. J. Physiol. 1959, *146* 133.

Isaacson, L. C., Modlin, M., & Jackson, W. P. U. Lancet 1963, 1, 946.

Jones, N. F., Clapham, W. F., Barraclough, M. A., & Mills, I. H. Clin. Sci. 1964, *26* 307.

Knudson, K. D., & Dahl, L. K. Postgrad. Med. J. 1966, *42* 148.

Mills, J. N., Thomas, S., & Williamson, K. S. J. Physiol. 1960, *151* 43p.

Moore, F. D. New Eng. J. Med. 1965, *273* 567.

Pickering, G. Circulation 1960, *21* 323.

Pitts, R. F. 'Physiology of Kidney and Body Fluids' Year Book Med Pub. Co. Chicago 1964.

Ibid 'Physiological Basis of Diuretic Therapy', C. C. Thomas Pub. Springfield, 1959.

Robinson, M. F., & Watson, P. E. Brit. J. Nutr. 1965, *19* 225 and 237.

Selkurt, E. E. Circulation, 1951, *4* 541.

Selkurt, E. E., Hall, P. W., & Spencer, M. D. Am. J. Physiol., 1949, *159* 369.

Thompson, D. D., & Pitts, R. F. Am. J. Physiol., 1952, *168* 490.

Tobian, L. Phys. Rev. 1960, *40* 280.

Wang, P., Marshall, R. J., and Shepherd, J. J. J. Clin. Invest. 1960, *39* 1051.

Welt, L. G. In 'Diseases of Metabolism' Ed. G. G. Duncan, P482 Saunders, 1964.


# Of Opium

Two hundred years ago William Patten, an undergraduate member of the Society, gave his dissertation on the subject of opium. He described how the drug might cause rarefaction of the blood, with consequent distension of the arterioles (especially in the brain) so that they "must obviously compress the nervous tubules, in a ratio of their distensions, and the nerves being too much compressed will permit a smaller quantity of animal spirits to be sent to the several parts of the body; hence all their actions must be weakened and numbed." How much nearer the truth are we today?

# CHANGING CONCEPTS OF THE CAUSE OF DIABETES MELLITUS

*by*

*L. J. P. DUNCAN, B.Sc., M.R.C.P.(Ed.) M.R.C.V.S.*

*and*

*B. F. CLARKE, M.B., M.R.C.P.(Ed.)*

**Diabetic & Diabetic Department, Royal Infirmary of Edinburgh.**

## INTRODUCTION

Probably the first allusion to diabetes is contained in the papyrus Ebers, dated at about 1500 B.C. and the symptomatology of the disorder was described by Aretaeus in the 1st century A.D. Prior to the late 17th century the causation of diabetes was variously ascribed to excessive food, alcohol, sex or grief or to maladies of the stomach, arteries, blood, nervous and other systems. However, in 1683 the Swiss Brunner recorded that pancreatectomised dogs displayed great thirst and polyuria before dying in coma, and in 1788 Cawley reported destruction of the pancreatic tissue in a patient dying of diabetes. These observations were largely disregarded until further evidence of a possible relationship between diabetes and the pancreas was provided by the classical experiments of von Mering and Minkowski in 1890. Twenty years earlier Langerhans, when aged 20, had described the islets to which his name was given in 1893 by Laguesse who was the first to suggest that they might produce an internal secretion. Schafer in 1895 considered that this secretion might profoundly modify the carbohydrate metabolism of the tissues and the name "insuline" was proposed by de Meyer in 1909. About 1900 Opie, in the U.S.A. and Ssobolew in Russia described hyaline changes in or destruction of the islets of Langerhans in diabetics and experimental proof that diabetes was possibly due to defective function of islet cells was provided by McCallum in 1909. He showed that ligation of the pancreatic duct, which caused atrophy of the exocrine pancreatic tissue, was not followed by diabetes but that subsequent destruction of the islet tissue resulted in the appearance of the disorder.

The first suggestion that diabetes in man might be an inherited disorder derives from the observations of Morton in 1696 who noted an extremely high prevalence of the disorder in certain families and this concept was established by von Naunyn in the early years of this century.

Banting and Best in 1921 successfully extracted active insulin from the islet tissue of dogs' pancreas and subsequently demonstrated that it reversed at least the major metabolic changes in experimentally diabetic dogs and in diabetic patients. This seemed in the 1920's to have shown idiopathic diabetes to be due to a simple failure of the beta cells to secrete insulin either because of an inherited functional defect or structural changes in the pancreatic islets.

In the next two decades experimental work in animals demonstrated the influence of other hormones on diabetes. Thus Houssay and his colleagues showed that hypophysectomy ameliorated the diabetes of pancreatectomised

animals, and Long and Lukens found adrenalectomy to have a similar effect. In 1927 Johns et al demonstrated that injection of an extract of the anterior pituitary gland could cause hyperglycaemia and ten years later Young and his associates induced permanent diabetes in dogs by repeated injections of this material; in these diabetic animals beta cell changes occurred and in later years Young attributed this effect to growth hormone contained in the pituitary extract. However, the simplicity and consequent attractiveness of the hypothesis that idiopathic diabetes was due to inadequate insulin secretion was such that this view continued to be held until the mid 1950's. By then, several techniques had been evolved to assay the insulin-like activity of plasma and pancreatic extracts. These led, in the next few years, to remarkable advances in the understanding of insulin metabolism, the factors inducing its release from the pancreas, its effect on the liver, its enzymatic destruction, its distribution throughout the body and the forms in which it is present in the blood. Of particular importance, however, was the demonstration that the plasma of obese diabetics often contained excessive quantities of insulin or insulin-like activity. Furthermore in insulin-dependent diabetics accidentally killed early in the course of the disorder, the islets were not only hypertrophied but sometimes contained normal or increased amounts of extractable insulin. These observations suggested that the primary abnormality of idiopathic or essential diabetes lay outwith the pancreas and was not a simple failure of insulin secretion.

The early view, proposed by Mirsky, that unduly rapid destruction of insulin by insulinase (glutathione insulin transhydrogenase) accounted for the apparent reduction of the hormone's activity in diabetes is no longer tenable; however, the concepts that diminished insulin activity might be due to its abnormal binding to protein in the plasma or the cell membrane or to the presence in the blood of anti-insulin factors or antagonists require further consideration. In addition there is the possibility that diabetes may be a genetically determined abnormality of messenger R.N.A. leading to the production of insulins with altered molecular structure and activity. These possibilities are discussed below along with the glucose-fatty acid cycle of Randle and more recent views concerning the genetics of the disorder. Ref. 1.

#### HEREDITY

Studies of the prevalence of overt diabetes and impairment of glucose tolerance in the relatives and families of diabetics have unequivocally revealed an inherited predisposition to develop the disorder. Thus, several investigations of twins, one of whom was diabetic, showed that the chances of the other twin having diabetes were about 85% if he was an identical twin and 30% if not identical.

However, the question of the mode or pattern of genetic transmission has only been seriously tackled since the early 1930's. At that time Pincus and White found that the prevalence of diabetes among the offspring of two parents, neither or one or both of whom was diabetic, approximated to a ratio of 1 : 2 : 4, respectively, which suggested that the disorder was inherited as a simple mendelian recessive with a penetrance of about 15-20% (i.e. that only 15-20% of those who were genetically liable to become clinically diabetic did so during their lifetime.)

Although this hypothesis was supported by the studies of Steinberg and Hanhart others have interpreted their own investigations to show either a dominant, a sex-linked, or in the case of juvenile-onset diabetics a recessive and in older-onset diabetics a dominant-type of inheritance. However, as pointed out by Clarke, it is rare for a common disease to be transmitted by a single gene and by postulating incomplete penetrance it is possible to prove almost anything in genetics. In consequence it is not surprising that more recent studies suggest that diabetes is dependent on several genes (i.e. is multifactorial); this might include the dominant transmission of the synalbumin-antagonist as discussed below. Thus, although idiopathic or essential diabetes is undoubtedly a genetically determined disorder much more information is required to establish the mode of its transmission. (Refs. 2. 3. 4. 5.)

#### GROWTH HORMONE

The possibility that excessive secretion of growth hormone might be causally associated with the appearance of diabetes was based on the following observations: (1) a period of apparently very rapid growth sometimes preceded the appearance of the disorder in young persons, (2) pregnancy occasionally precipitated permanent or temporary diabetes, (3) the

repeated injection of growth hormone — albeit in exceedingly large doses — caused diabetes in dogs and (4) diabetes occurs in acromegalic patients (although in only 20-30% of them). The hypothesis was given further support by the reported finding of increased plasma growth hormone in diabetics; however, the assay method used was unsatisfactory and more recent use of the sensitive and accurate radioimmunoassay has shown no evidence of excess secretion of growth hormone either under basal conditions or in response to secretogenic stimuli in diabetics or pre-diabetics. (Ref. 6, 7).

#### ANOMALIES OF THE GLUCOSE-FATTY ACID CYCLE

Randle and his colleagues have suggested that one of the earliest, if not the primary, causes of diabetes was a defect of the glucose-fatty acid cycle resulting in the increased release of triglycerides and free fatty acids which reduce both the uptake of glucose by muscle and the effect of insulin on the tissues. This suggestion was based firstly on the fact that fasting, which induces release of these lipids, causes impaired glucose tolerance and relative insulin insensitivity and secondly on observations made on normal subjects and obese mild diabetics fed various types of diets and subjected to a glucose tolerance test. The possibility that the initial excess release of the lipids might be due to increased growth hormone activity was also raised since this hormone has these metabolic effects; more recently a lipolytic hormone derived from the pituitary has been identified and there is some evidence that it may be increased in diabetes. However there are many clinical and experimental observations which cannot be reconciled to this hypothesis. Moreover, among the earliest changes in metabolism that follow upon inadequate insulin activity is fat mobilisation with release of triglycerides and fatty acids; thus these latter changes are likely to be secondary rather than primary in relation to the cause of diabetes. (Ref. 8, 9).

#### INSULIN ANTAGONISTS

Insulin antibodies, although they may act as insulin antagonists, are found only in patients taking exogenous insulin. However, from evidence obtained in a series of studies dating from 1955, Vallance-Owen and his colleagues have carefully developed a hypothesis that at least one of the fundamental causes of diabetes is the presence in excess of a plasma albumin-bound insulin antagonist. They demonstrated that the albumin fraction of the plasma proteins of non-diabetics inhibited the effect on the rat diaphragm of 1,000 milli units/ml. insulin in vitro; this antagonism was marked when the albumin was present in concentrations of 3.5% or more (i.e. within or above the physiological range) but was lost in concentrations of 1.25% or less. However, the albumin fraction of plasma of patients having diabetes, irrespective of its severity, and of pre- or sub-clinical diabetics was strongly antagonistic at this lower concentration. By various techniques they were able to show that the albumin itself had no inhibitory effect and that the antagonistic property was due to a polypeptide substance associated with but separable from the albumin — this being termed the "synalbumin antagonist". An important finding was that the plasma of patients having "secondary" diabetes due to primary disease (e.g. haemochromatosis) or removal of the pancreas did not contain excess synalbumin. Further studies have shown this synalbumin-antagonist to have many physico-chemical similarities to the B chain of insulin and some support to this suggestion has been provided by the demonstration that albumin — B chain, prepared by incubating B chain with non-antagonistic albumin, is markedly antagonistic to insulin in vitro. However, insulin antagonism has not been demonstrated in vivo following the injection of B chain.

Since it is not unusual for a biochemical reaction to be inhibited by a substance which chemically resembles that which accelerates it, it is not inconceivable that the B chain, released by reductive cleavage of the parent molecule under the influence of insulinase, might antagonise the effect of endogenous insulin and thus bring about diabetes. However, synalbumin is present in the plasma of normal persons so that if this substance is the cause of diabetes then the disorder must result from an exaggeration of a normal phenomenon. Whether or not carbohydrate intolerance or frank diabetes develops and the severity of the diabetes should it occur, will depend on the amount of insulin antagonist present and the degree to which the beta cells can compensate by producing more insulin. It is of considerable interest that even in severe diabetics, hypophysectomy results in the disappearance of the synalbumin antagonist which may explain the considerable fall in insulin requirement and, perhaps, the ameliorating effect of this procedure on certain types of diabetic

retinopathy. It has also been reported that synalbumin positivity occurs much more frequently in the relatives of diabetics than of non-diabetics; if synalbumin positivity is a valid biochemical marker or indicator of the inherited diabetic diathesis then the disorder would seem to be transmitted as a mendelian dominant having a low degree of penetrance.

However, hypotheses related to the B chain albumin-linked antagonist require further proof; and of some importance is the fact that the antagonist does not inhibit the effect of insulin on adipose tissue and there are no studies of its influence on insulin's activity on the liver which is certainly one of the most important organs contributing to the metabolic defects in diabetes. (Refs. 6, 10, 11).

#### FREE, BOUND AND ABNORMAL INSULINS

Although the subject is still somewhat confused it would appear that insulin is present in the blood in two main physical forms. The first is that in which it is liberated by the beta cells; this is called free or typical insulin. In vitro it is active on both muscle and adipose tissue, and, because this activity is neutralised by insulin — antiserum, it is also called suppressible insulin. In its second form insulin is bound to a protein, is active on fat but not muscle and is not inhibited by antiserum; this form is termed bound, atypical or non-suppressible insulin. Since only free insulin is detectable in the pancreatic vein whereas both occur peripherally, it is suggested that binding occurs in the liver. In non-diabetics the ratio of free to bound insulin in the plasma varies according to the metabolic state and needs of the body; for example in fasting most of the insulin is present in bound form and after meals in free form. Several authorities, in particular Antoniades, have postulated that diabetes may be due to excessive insulin binding or an inability to convert bound into free insulin. Certainly the plasma of obese persons with mild diabetes contains an excessive proportion of bound insulin even after the administration of glucose. Since the albumin-bound insulin antagonist, discussed above, does not inhibit insulin activity on fat this factor may be associated with the difference in metabolic activity between free and bound insulin. Recent work by Cahill and his colleagues, however, suggests that in vivo only free insulin can pass into the extra-vascular fluids and thus be able to come into contact with and influence the metabolism of peripheral tissue cells; thus an absolute reduction of free insulin, brought about by excessive binding of the remainder may be causally related to the metabolic disturbance.

Insulinase, not only promotes the reductive cleavage of the disulphide bonds of insulin to release its A and B chains but can also bring about their reconjugation. The possibility has been raised that a genetic defect of this enzyme's activity might promote abnormal re-conjugation of the A and B chains resulting in new forms of insulin having either no activity or possessing antigenic properties. However, to date no consistent abnormality in the chemical structure of insulin in human diabetes has been detected. (Refs. 12, 13, 14, 15.)

#### ROLE OF THE PANCREAS

The elucidation of the chemical and molecular structure of insulin by Sanger raised the possibility that diabetes might be due to the production of abnormal insulins; the protein synthesis of insulin is under the influence of messenger R.N.A., the form of which is genetically determined. However, there is as yet no evidence to support such a hypothesis.

Although the initial cause or causes of the metabolic abnormalities in diabetes is not a primary reduction in insulin secretion but rather a failure to produce enough extra insulin to overcome factors, of extra pancreatic origin, which diminish its effective activity, it must be remembered that secondary exhaustion of the beta cells can occur with decreasing capacity and eventual inability to produce insulin. This explains why diabetes controlled by diet alone may, after some years, require treatment with a sulphonylurea (which uncouples insulin from inactive protein-bound complexes), why secondary-sulphonylurea failure occurs and the efficacy of the diguanides (which potentiate the effect of insulin on the tissues) in such patients, and, of course, the development of ketoacidosis when insulin therapy is discontinued in insulin-dependent diabetics. Thus although the primary cause of diabetes lies outwith the pancreas, the metabolic severity of the established disease depends very largely on the capacity of the beta cells to respond to the challenge; like a tired horse they may be flogged to death.

Finally it is necessary to consider obesity, pregnancy, stress and injury which are sometimes listed as causes of diabetes. They are

not causes of the disorder but may precipitate its overt clinical manifestations in those who are genetically pre-disposed to diabetes. (Ref. 16.)

*REFERENCES*

For the sake of simplicity and because a complete bibliography would be too long the references given at the end of each section are limited to the more recent papers and works relevant to the subject matter therein considered.


1. Papaspyros, N. S. The history of diabetes mellitus. George Thieme Verlag. Stuttgart. 2nd Ed. 1964.
2. Bigozzi, V., and Teodori, V. Acta diabetologica Latina 2, 275, 1965.
3. Clarke, C. A. in Diabetes Mellitus. University of Edinburgh Press, 1966, Page 103.
4. Neel, J. V., Fajans, S., Conn, J. W., Davidson, R. T.; Diabetes Mellitus — Genetics and Epidemiology of Chronic Diseases. U.S. Department of Health. Washington 1965.
5. Simpson, N. E. Diabetes 13, 462, 1964.
6. Berson, S. A., and Yalow, R. S. Diabetes 14, 549, 1965.
7. Hunter, W. M., Clarke, B. F., and Duncan, L. J. P. Metabolism 15, 596, 1966.
8. Randle, P. J., Garland, P. B., Hales, C. N., Newsholme, E. A. in Ciba. Found. Coll. Endocr. Churchill 15, 192, 1964.
9. Anselmino, K. J., and Hoffmann, F. Dtsch. med. Wschr. 90, 1697, 1965.
10. Vallance-Owen, J. in Diabetes Mellitus. University of Edinburgh Press, 1966, page 21.
11. Sherman, L. Diabetes 15, 149, 1966.
12. Keen, H. in Diabetes Mellitus. University of Edinburgh Press, 1966, page 1.
13. Antoniades, H. N., Bougas, J. A., Camerini-Davalos, R., and Pyle, H. M. Diabetes 13, 230, 1964.
14. Pasio, E. A., Soeldner, J. S., and Cahill, G. F. Diabetologia 1, 125, 1965.
15. Williams, R. H. Ann. int. Med. 63, 512, 1965.
16. Duncan, L. J. P., and Clarke, B. F. Ann. Rev. Pharmacol. 5, 151, 1965.


## DIAGNOSTIC PROBLEM

**Subject :**

J.W., Male, Age 28; Rubber works employee.

**Presenting Complaint :**

Abdominal colic and constipation.

**History of Complaint :**

Over the past six months J.W. has suffered from attacks of abdominal colic. These have been increasing in frequency and severity; they now occur about twice per week, and are not in any way related to time of day or to food of any type. The pain is unrelieved by food, alkali or warmth. During an attack the pain is central abdominal of a colic type, and may last for up to two hours.

He has also complained of anorexia over the past two months; and generalised weakness, especially in the grip of his hands, has become evident.

**Past history :**

Usual childhood illnesses.

**Social history :**

Not relevant.

**Family history :**

No history of any familial diseases.

**Examination :**

No obvious jaundice or cyanosis. Marked pallor of mucous membranes and a pale complexion.

C.V.S. — Pulse 84. Regular in time and force. Apex beat in 5th interspace, within M.C.L. Heart sounds I and II. No murmurs.

R.S. — No abnormality detected.

G.I.S. — Tongue and fauces clean.
Dark line around gum margins.
Abdomen moves with respiration. No visible veins, peristalsis or masses.
No guarding. No tenderness either direct or rebound.
No masses palpable. Liver not enlarged.
Spleen and kidneys not palpable.

C.N.S. — No loss of function detected in cranial nerves.
No sensory peripheral loss.
Slight bilateral weakness of hand grip.
No obvious muscle wasting.

**Findings :**

1. History of abdominal colic, constipation, anorexia and weakness.
2. Pallor of mucous membranes.
3. Darkening of gum margins.
4. Weakness of grip.

What is the diagnosis? How would you confirm it? How would you treat it?

See page 56.

# POLYCYTHAEMIA

A. W. DELLIPIANI, M.B., M.R.C.P.E.

Lecturer, University Department of Therapeutics, Royal Infirmary, Edinburgh.

Though strictly speaking polycythaemia means an increase in all three formed elements in the peripheral blood the term is usually used to describe an increase above normal in the number of circulating red cells per unit volume of blood. The polycythaemia may be relative, due to a fall in the plasma volume, or true or absolute when the total number of red cells in the body, the red cell mass, is increased. Such an increase in the mass of circulating red cells could in theory be produced by a prolongation of the average life span of red cells beyond the normal value of about 110 days, or by an increased output of red cells by the haemopoietic system. Present evidence indicates that in the majority of true polycythaemic syndromes, it is the latter which occurs (Pike 1958).

## SOME COMMENTS ON AETIOLOGY AND PATHOGENESIS

Before discussing this further a brief word about the normal control of erythropoiesis would seem appropriate. In health the number of red cells in the blood stream remains remarkably constant and though it is known that endocrine secretions from the gonads, the thyroid and the suprarenals have considerable influence on this, they do not seem to supply the fundamental stimulus to erythropoiesis (Wintrobe 1961). For many years, however, clinical and experimental observations in man and animals have shown the importance of oxygen; thus oxygen lack has a stimulating effect and excess of oxygen depresses erythropoiesis. That this is not a direct effect on erythropoiesis was shown by the fact that in parabiotic rats erythropoiesis occurs in both rats even if only one of them is made anoxic (Reissmann 1960) and it can also be shown that the plasma of anaemic animals contains a factor capable of stimulating erythropoiesis. This and similar work supported earlier suggestions of the existence in the blood of a hormone-like substance capable of stimulating erythropoiesis. This factor, erythropoietin, is now usually accepted as the main humoral mechanism in the control of erythropoiesis. It has no effect on leucocytes and platelets. The main source of erythropoietin is probably the kidney but an extra renal site of this or a similar hormone, probably in the liver, exists also (Rosse and Waldmann 1962).

Under normal conditions it is presumed that the oxygen tension in the blood controls the release of erythropoietin which is capable of stimulating the marrow to produce red cells only. Any rise of the number of red cells above normal is counteracted by the tendency for such a change to depress the output of erythropoietin.

## POLYCYTHAEMIA VERA

This is the earliest of these conditions to be described. Original descriptions are those of Vaquez (1892) and Osler (1903). In contrast to the other polycythaemic syndromes to be discussed, in the classical case there is evidence

of hyperplasia of all marrow elements, with leucocytosis and thrombocytosis in addition to erythrocytosis, and also splenomegaly.

The aetiology is a subject which gives rise to much discussion and though many would agree with the view put forward by Damashek (1954) that it is a relatively benign neoplasm, there has been a tendency to challenge this in the light of the recent progress made in the field of secondary polycythaemias (Pike 1958). The neoplastic concept classifies polycythaemia vera as one of the group of "myeloproliferative syndromes" which includes myelofibrosis, chronic myeloid leukaemia, primary thrombocythaemia and di Guglielmo's syndrome, all these conditions being thought to have common ancestry in the primitive multipotential mesenchymal cell. In favour of this concept is the fact that intermediate forms with features characteristic of several of the clinical entities constituting the group may be seen quite frequently in the same patient and that one condition may evolve into another (Lopas and Josephson, 1964). An increase in basophil granulocytes is a common feature in these conditions which also appear to respond to the same type of therapy. Much of the evidence in support of the myeloproliferative concept of the aetiology of polycythaemia vera it will be appreciated, is largely circumstantial and other aetiological possibilities will be mentioned later.

#### SECONDARY POLYCYTHAEMIA

In the light of the known physiological importance of oxygen in the control of erythropoiesis it is not surprising that a group of well defined conditions exist where tissue anoxia due to a low oxygen saturation in the blood results in polycythaemia. This may result from a low oxygen tension in the inspired air as occurs for example as part of the adaptive mechanism to high altitude. Pathological causes include various diseases of the lungs and heart, especially congenital cyanotic heart disease and arterio-venous shunts which allow unsaturated venous blood to enter the arterial circulation. Hypoventilation not necessarily due to lung disease as caused by extreme obesity or structural chest disease, may also cause secondary polycythaemia which may also result from the presence of abnormal blood pigments.

In 1945 Fairly described two cases of polycythaemia treated by removal of a renal carcinoma and subsequent developments have confirmed the association of polycythaemia with various well defined lesions of the kidney, benign and malignant tumours, cysts and hydronephrosis, and of other organs also, such as cerebellar haemangioblastoma, phaeochromocytoma, hepatoma and possibly certain uterine tumours (Pike 1958). The association is particularly strong with hypernephroma and polycythaemia will be found in about 30-50 per cent of patients suffering from this condition (Penington 1965). Raised levels of erythropoietin may be found in the plasma of patients with anoxic polycythaemia and in patients with renal lesions, cerebellar haemangioblastoma and phaeochromocytoma (Gurney 1965, Modan 1965).

Polycythaemia has also been noted to arise as a result of the action of various poisons. The best evidence for such a causation is the polycythaemia which may follow cobalt poisoning. This is not related to the erythrocytosis which may follow the treatment of pernicious anaemia. For further information on this subject the reader should consult a recent review by Modan (1965).

In the light of the known causes of secondary polycythaemia the possible roles of anoxia and erythropoietin in the aetiology of polycythaemia vera have been scrutinised recently and although anoxia seems to have been excluded without difficulty, the status of erythropoietin in polycythaemia vera remains undecided (Gurney 1965). If the red cell production in polycythaemia vera is due to primary proliferation in the bone marrow as suggested by the myeloproliferation concept of the disorder one would expect the serum levels of erythropoietin to be depressed in that condition. Unfortunately the measurement of erythropoietin depends on biological assay methods which are relatively crude. Thus anything less than a twofold rise in the circulating level of erythropoietin cannot be reliably detected and it is known that less than this is capable of producing polycythaemia (Penington 1965). It is also known that the sensitivity of different individuals to erythropoietin varies. Even the best methods at present available are only able to demonstrate equivocal levels in normal man. It seems therefore that present methods cannot definitely exclude raised erythropoietin levels in polycythaemia vera and certainly cannot demonstrate reduced levels. However, even if erythropoietin could be implicated as a causative feature of the erythrocytosis of polycythaemia vera, some other hormone would

have to be responsible for the leukocytosis and thrombocytosis commonly associated with that condition.

Another approach to the problem has been to see if there is any association between polycythaemia vera and any of the lesions known to be responsible for secondary polycythaemia. Delamore and Macdonald (1962) in a study of patients with polycythaemia vera, demonstrated no pyelographic abnormality but Brandt and his colleagues (1963) in a larger series of patients with polycythaemia vera found that 9 per cent of cases had significant lesions with included two renal carcinomas.

#### BENIGN ERYTHROCYTOSIS

In dealing with polycythaemia one is left with a group of patients with true polycythaemia without leukocytosis or thrombocytosis and without splenomegaly. In all respects the blood picture simulates that of secondary polycythaemia yet there is no clinical or laboratory evidence to support this. It has been suggested (Modan 1965) that this group should be classified separately. Some of these patients turn out to have polycythaemia vera and some perhaps to have polycythaemia secondary to an unrecognised cause. Most of the so-called cases of polycythaemia vera described in children belong in this group (Abildgaard et al 1964). Familial cases associated with splenomegaly can be classified here. Some individuals with erythrocytosis of this type may be cases with high normal blood counts. Apart from those patients who turn out to have polycythaemia vera, the main characteristic of this group of conditions is their benign course.

#### RELATIVE POLYCYTHAEMIA

In this condition the red cell values appear to be raised but are in fact normal or even reduced. The apparently high counts are the result of a considerably diminished plasma volume. In most cases the cause of this haemo-concentration such as burns, diuresis, dehydration, is obvious. In 1952 Lawrence and Berlin described a group of cases in which the red cell mass was normal and the plasma volume chronically depressed giving rise to apparent erythrocytosis. They called this polycythaemia of stress mainly because the haemo-concentration simulated that which occurs initially on being exposed to the stress of high altitude (Lawrence 1952). Damashek (1953) emphasised the association of this condition with anxiety and tension, vascular disease, hypertension and peptic ulceration. In that the association with stress is only inferred the condition is probably better labelled as pseudopolycythaemia; there is well documented evidence that it is not uncommon and certainly commoner than polycythaemia vera. It runs a more benign course and like polycythaemia vera is commoner in men.

It is likely that many of the cases of polycythaemia hypertonica which Gaisbock described belong to this group (Gaisbock 1922). This interesting group is the subject of two recent reviews where it was found that although some patients with the features of Gaisbock's syndrome had a true though mild polycythaemia, many had pseudopolycythaemia (Russell and Conley 1964; Hall 1965).

In the light of the preceding discussion the following classification somewhat modified after Modan (1965) is suggested.

TABLE I

*True Polycythaemia*

1. Polycythaemia vera.
2. Secondary Polycythaemia.
   (a) *Anoxic*
   - High altitude
   - Lung Disease
   - Heart Disease—congenital or acquired
   - Respiratory disease
   - Obesity
   - Abnormal haemoglobin pigments

   (b) *Humoral*
   - Renal
   - Cerebellar haemangioblastoma
   - Phaeochromocytoma
   - Uterine myoma (?)
   - Liver carcinoma
   - Endocrine—Cushing's syndrome
   - Others

   (c) *Chemical and Toxic*

3. Benign erythrocytosis
   - Idiopathic
   - Familial
   - Primary erythrocytosis of children
   - Normal variant.

*Relative Polycythaemia*

1. Fluid loss or diminished intake.
2. Pseudopolycythaemia or polycythaemia of stress.

## DIAGNOSIS

Space does not permit a full description of the clinical features of these conditions. Certain diagnostic difficulties are worth discussion. The main problems which often arise can be stated as (a) Does the patient have polycythaemia and (b) if so, is this true or relative polycythaemia, and, if the former, is the physician dealing with polycythaemia vera or a secondary type?

Laboratory determinations will usually enable the diagnosis of polycythaemia to be made and a packed cell volume of > 55% (> 52% in the female) establishes the diagnosis. However, this may be masked in true polycythaemia by the fact that the red cells tend to be small. Determination of the red cell count will distinguish these cases. Occasionally the plasma volume may rise in proportion to the red cell mass masking both the rise in the red cell count and the packed cell volume. The reason for this may not be obvious but a not unusual cause is congestive cardiac failure. Bleeding, a common complication of polycythaemia vera for example where there is a bleeding tendency and where 10-15 per cent of patients have a peptic ulcer, may also mask the diagnosis. In difficult cases clinical suspicion may only be confirmed by an actual measurement of the red cell mass. The most popular method of doing this is with the use of the radioactive isotope chromium$_{51}$ (Mollison 1961).

If in association with polycythaemia there is leukocytosis, thrombocytosis, splenomegaly, hyperplasia of red and white cell and platelet precursors in the bone marrow and a raised leukocyte alkaline phosphatase, then the patient has polycythaemia vera. All cases are, however, not typical. Thus about 30 per cent of cases may have normal white and platelet counts and in a similar proportion the spleen is not palpable. The marrow is not always hyperplastic. It is in this group that the possibility that one is dealing with pseudopolycythaemia arises and once this has been excluded by determining the red cell mass, secondary polycythaemia is likely.

Though an anoxic polycythaemia is usually clinically obvious this is not always so and in particular a pulmonary arterio-venous shunt may be overlooked. Determination of the percentage oxygen saturation of the arterial blood is the only way of excluding this group with certainty. This should normally be not less than 97%. In older patients with polycythaemia vera levels of 93% have been described. There are some cases of polycythaemia vera however where unexplained levels of 91% have been found. A low level in this condition may occasionally be due to a throbotic complication in the central nervous system resulting in hypoventilation (Bader et al 1963). Intravenous pyelography and occasionally aortagraphy will be necessary to distinguish renal causes of polycythaemia and in fact in view of the findings of Brandt and his colleagues (1963) should be considered even in typical cases of polycythaemia vera. The leukocyte alkaline phosphatase is of considerable help in distinguishing vera from secondary types of polycythaemia. In the latter cases it is not raised. Infection should be remembered however as one of the commoner conditions giving rise to abnormally high levels (Hayhoe 1958). At present the determination of the circulating level of erythropoietin is too difficult and too insensitive to be used routinely in diagnosis but should be considered in selected cases.

Some cases will defeat all attempts at an accurate diagnosis particularly when facilities for red cell mass determination are not available. Observation over a period of time with perhaps appraisal of the response to careful venesection will help in most cases.

## COURSE AND PROGNOSIS

Though cases of polycythaemia vera have been known to live for many years without complications, this is rare even with treatment. Vascular thrombosis is the most frequent complication and haemorrhage is not unusual although the precise mechanism for this is not understood. In that the disease is one of later life, affected subjects may die of an unrelated condition. The terminal picture of the disorder may be myelofibrosis, a leukaemoid reaction which resembles chronic myeloid leukaemia, or acute leukaemia. Untreated the mean survival is about five years from the time of diagnosis (Lancet 1965). The course of secondary polycythaemia depends largely on the underlying cause.

## TREATMENT

Except in polycythaemia vera there is little evidence that therapy is required in the other conditions in this group. Even though the

blood viscosity will be raised in these there is little evidence that this alone requires therapy and thus, for example, vascular phenomena are said on the whole to be unusual in the secondary physiological polycythaemia of high altitude (Russell and Conley 1964). The situation may, however, be different where there is already a predisposition to vascular disease.

In polycythaemia vera some form of treatment is required. In particular treatment reduces the incidence of vascular accidents and the life expectancy is thought to be prolonged to about 13 years from the time of diagnosis (Massouredis and Lawrence 1957).

Venesection is the more frequently used form of treatment and by itself may produce a remission lasting several months. This is, however, unusual and when it is required more often than once in two months resort should be made to some other form of therapy. It is of particular value either alone or in conjunction with other treatment in a surgical emergency, for the rapid relief of symptoms and in patients not responding to or suffering from some complication of other therapy such as thrombocytopaenia. Five hundred millilitres of blood should be removed on alternate days.

The alternative to phlebotomy is some form of marrow depressant or a haemolytic agent such as phenylhydrazine. The latter drug does nothing to remedy the thrombocytosis and this and its toxicity make it very little used nowadays. The most popular marrow depressant has for many years been the isotope $P^{32}$. This is easily administered usually intravenously but it can be given orally, has a relatively short half life of 14 days, is a $\beta$ emitter and irradiates the marrow tissues by being incorporated into the actively dividing marrow cells and then into the bones as calcium phosphate. Radiation sickness does not occur and marrow depression is unusual. If one defines a remission as the disappearance of symptoms and the return of the blood counts to normal for at least six months, 84% of patients have a full remission, 50% requiring one dose only and less than 10% more than two doses (Szur et al 1959). Four per cent, however, fail to remit after three injections and 13% have partial remissions only. The average remission is of the order of two years though the range is considerable.

The main objections to $P^{32}$ are the danger of thrombocytopaenia or pancytopaenia and that it is thought to increase the incidence of acute leukaemia. In experienced hands the former is not a real problem but this does not appear to be so with the latter. The incidence of acute leukaemia was initially reported raised by Lawrence in 1955 and more recently Modan and Lilienfeld (1964) have put it at up at over 11 per cent. It is said, however, that acute leukaemia is merely the natural progression of the disease and becomes more obvious when survival is prolonged (Osgood 1964) and some well authenticated cases of acute leukaemia occurring in non-irradiated subjects have been reported (Szur et al 1959). Nonetheless a recent report of chromosomal abnormalities in potients who received $P^{32}$ is disturbing (Macdiarmid 1965) and though their relevance has been challenged (Millard 1965) they recollect the findings of Court Brown and Abbatt (1955) of chromosomal abnormalities in patients irradiated for ankylosing spondylitis in whom an increased incidence of acute leukaemia is accepted.

The main deficiency until recently has been the lack of a series of patients treated by other than $P^{32}$ but a recent series from Manchester of 127 patients treated with cytotoxic drugs remedies this (Perkins et al 1964). Two points in particular are of interest. Firstly none of these patients developed acute leukaemia, those patients not dying of some complication or intercurrent disease developing either myelofibrosis or a leukaemoid reaction simulating chronic myeloid leukaemia but distinguished from this by the absence of the Philadelphia chromosome and the normal alkaline phosphatase reaction. Secondly the mean survival was the same as for patients treated with $P^{32}$ i.e. about 13 years (Perkins et al 1964; Halnan and Russell 1965).

The drugs used in the main were thiotepa, busulphan and the folic acid antagonist pyrimethamine the last two being considered the drugs of choice. Though a relatively small dose of pyrimethamine was used (25mgs daily) 30% of patients had complications in the form of megaloblastic anaemia and thrombocytopaenia, though anorexia, nausea, buccal ulceration and exfoliative dermatitis could occur. These of course are readily reversible with folic acid but treatment necessitates close supervision. Remissions were of the order of 10-12 months. Susulphan was given in a dose of 2-4mgs daily with a maintenance dose of 2mgs once or twice weekly, i.e. doses tended to be smaller than those used in the treatment

of chronic myeloid leaukaemia. Thrombocytopaenia was a problem and 8 of 18 patients did not respond. Six had remissions of 12-30 months.

On the whole the experience of drug therapy appears to be that it is more difficult to apply, necessitates more supervision and that remissions are shorter. Since the survival of patients on drugs is in general similar to that of those on $P^{32}$ it does not seem to matter what one uses providing one uses something but it is possibly wiser to avoid $P^{32}$ in the younger patient with polycythaemia vera.

*REFERENCES*


Abildgaard, C. F., Cornet, J. A., and Schulman, I. J. Pediat. 1964, *63*, 1072.

Bader, R. A., Bader, M. E., and Duberstein, J. L. Amer. J. med. 1963, *34*, 435.

Brandt, P. W. T., Dacie, J. V., Steiner, R. E., and Szur, P. Brit. Med. J. 1963, *2*, 468.

Court Brown, W. M., and Abbatt, J. D. Lancet, 1955, *2*, 1382.

Damashek, W. Blood, 1953, 8, 282.

Damashek, W. Bull N.E. med Center, 1954, *16*, 53.

Delamore, I. W., Macdonald, A. F., and Samuel, E. Brit. J. Radiol. 1962, *35*, 671.

Firly, K. D. Roy. Melb. Hosp. clin. Rep. 1945, *16*, 47.

Gaisbock, F. Ergebn. inn. Med. Kinderheilk. 1922, *21*, 204.

Gurney, C. W. Annu Rev. Med. 1965, *16*, 169.

Hall, C. A. Arch. intern. Med. 1965, *116*, 4.

Halnan, K. E., and Russell, M. H. Lancet, 1965 *2*, 760.

Hayhoe, F. G. J., and Quaglino, D. Brit. J. Haemat. 1958, *4*, 375.

Lancet, 1965, *1*, 849.

Lawrence, J. H. Acta. med. Scand. 1952, *192*, 117.

Lawrence, J. H. Polycythaemia, Physiology, Diagnosis and Treatment, N.Y. 1955.

Lawrence, J. H., and Berlin, N. I. Yale J. Biol. Med. 1952, 24, 498.

Lopas, H., and Josephson, A. M. Arch. intern. Med. 1964, *114*, 754.

MacDiarmid, W. D. Quart. J. med. 1965, *34*, 133.

Massouredis, S. P., and Lawrence, J. H. Amer. J. med. Sci. 1957, *233*, 268.

Millard, R. E. Lancet, 1965, *1*, 1116.

Modan, B. J. Chron. Dis. 1965, *18*, 605.

Modan, B., and Lilienfeld, A. M. Lancet, 1964, *2*, 439.

Mollison, P. L. Blood Transfusion and Clinical Medicine. Third Edition. Blackwell Scientific Publication, 1961, p.62.

Osgood, E. E. Lancet, 1964, *2*, 967.

Osler, W. Amer. J. med. Sci. 1913, *145*, 595.

Penington, D. G. Proc. Roy. Soc. Med. 1965, *7*, 488.

Perkins, J., Israels, M. C. G., and Wilkinson, J. F. Quart. J. med. 1964, *33*, 499.

Pike, G. M. New Engl. J. med. 1958, *258*, 1250; 1297.

Reissmann, K. R. Blood, 1960, *16*, 1401.

Rosse, W. F., and Waldmann, T. A. Blood, 1962, *19*, 75.

Russell, R. P., and Conley, C. L. Arch. intern. Med. 1964, *114*, 734.

Szur, L., Lewis, S. M., and Goolden, A. W. G. Quart. J. med. 1959, *28*, 397.

Vaquez, H. Comp. rend. Soc. de biol. 1892, *4*, 384.

Wintrobe, M. M. Clinical Haematology. Fifth Edition. Henry Kimpton 1961, p.47.


## THE CONTRIBUTORS

DR. J. B. STANTON *is Physician in charge of Neurology at the Northern General Hospital. He is co-author of the chapter on Psychiatry in Davidson's Medicine and co-author of "The E.E.G. in Clinical Practice".*

DR. L. J. P. DUNCAN *is Physician in charge of the Diabetic and Dietetic Department of the Royal Infirmary. He has published numerous originals and reviews on various aspects of diabetes and is editor of the recently published symposium, "Diabetes Mellitus".*

DR. A. W. DELLIPIANI *is a former Editor of Res Medica and former president of the Royal Medical Society. He is at present a lecturer on the staff of the Therapeutics Department. He has published several papers on diseases of blood.*

DR. M. K. MCDONALD *is a Senior Lecturer in Pathology. She has pioneered electron microscopy studies of the kidney in this University, and is an authority on this aspect of Renal Pathology. In addition to many research papers she has contributed chapters to "Colloquia on Endocrinology" and "Diabetes Mellitus".*

DR. JOHN HABESHAW *is a first class honours graduate in Pathology and was a leading figure in Society debates last session. He is at present working in Cornwall and will shortly return to Edinburgh to take up a career in Pathology.*

DR. NIGEL STOTT *is a first class honours graduate in Pathology and winner of the Conan Doyle prize. He has returned to work for some months in his native South Africa.*

# RESEARCH TOPIC

## AN INVESTIGATION INTO THE SPECIFICITY OF ANTIPLATELET SERUM PREPARED IN RABBITS

This summer I spent six weeks in the Immunopathology Laboratory in the Pathology Department of the University, investigating this antiplatelet serum. This antiserum had been prepared by multiple immunisation of several rabbits with human platelets, and I was trying to find out, among other things, if this antiserum was specific for platelets, or if it reacted with other tissues and organs of the human body.

The main technique used for the serological investigations was gel diffusion in Ouchterlony plates. These are Petri dishes containing agar to a depth of about 4mm., in which wells may be cut in the required patterns. The "antigen", which in this case might be a suspension of disintegrated platelets, is placed in one well, and the "antibody", in this case antiplatelet serum, is placed in an adjacent well. Provided both reagents are in a diffusable state, they diffuse through the agar and a line of precipitate is formed where they are present in optimal proportions. This line is specific for this particular antigen/antibody reaction.

In some experiments antiplatelet serum and extracts prepared from various human organs and tissues such as bone marrow, liver, gastric mucosa and spleen were placed in adjacent wells, and in each case multiple lines were formed. The platelets used for immunising the rabbits were probably contaminated with serum proteins from the donors, and so the antiplatelet serum would contain, as well as antibodies to platelets, antibodies to these serum proteins. If this were the case, any serum proteins contaminating the platelets and organ extracts used in the experiments would combine with these antibodies, forming multiple lines. To get rid of these unwanted antibodies in the antiplatelet serum, the antiserum was adsorbed to normal human serum, which combined with the antiserum protein antibodies. The adsorbed antiserum was then more specific for platelets.

The results of these experiments indicate that platelets have "antigens" in common with several other organs and tissues of human origin, and hence that an antiserum prepared by immunisation with platelets contains antibodies against at least one component of other human tissues. The fact that platelets, as it were, represent other human tissues may prove useful in a test which it is hoped may be developed to assist in tissue transplantation.

At the moment the main work of the laboratory is concerned with tube tissue cultures of macrophages obtained from the peritoneal cavity of mice, and with the way in which these macrophages react to various things such as red blood cells when these are added to the cultures. My last set of experiments was to investigate how the macrophages reacted to platelets and if this reaction differed if the platelets had previously been incubated with antiplatelet serum. It was found that the platelets treated with the antiserum were phagocytosed, while the untreated platelets were rejected. Phagocytosis indicates that an antigen/antibody reaction of some kind has taken place.

At the moment the applications of these results are not clear, and as much still remains to be done on this subject they are largely a matter for speculation.

N. BAKER.

# ELECTRON MICROSCOPY IN GLOMERULONEPHRITIS

**M. K. McDONALD, M.B., Ch.B., F.R.C.P.(Ed.)**

**Senior Lecturer in Pathology, University of Edinburgh.**

Electron microscopy has been in use as a research tool for many years, and as such has helped to demonstrate and elucidate the fine structure of many organs, including that of the kidney. The intricate pedicel structure of the renal glomerular epithelial cell, the glomerular endothelial fenestrae (Fig. I) and the varying cytological arrangements in the tubular part of the nephron were all unknown before the advent of electron microscopy. As a development of this anatomical function of the microscope, the technique began to be applied to diseased tissues in an attempt to analyse further the relation of disordered structure to disordered function. This type of investigation held the inherent difficulty that human tissues to be examined in this way had, of necessity, to be biopsy material, since autolytic changes in post-mortem material are so gross that cytological ultrastructure is significantly destroyed.

Investigations were carried out in many human diseases where biopsy material was available, and in particular several diseases of the renal glomeruli became capable of more thorough description, classification and clinico-pathological correlation. It is probably not too much to say that the concept of glomerulonephritis itself was revolutionised.

## *EARLY CONCEPTS OF GLOMERULONEPHRITIS*

Before the advent of the electron microscope and the technique of renal biopsy the usually accepted classification of glomerulonephritis was that of Ellis, proposed in 1942; this had superseded the old classification elaborated by Volhard and Fahr, which divided the disease into three stages, acute, subacute and chronic. Ellis' classification, more clinically acceptable, described two separate disease processes. One was named Type I glomerulonephritis; this was of acute nature, clinically and pathologically, and usually resolved with complete clinical recovery. It might, however, progress to a chronic, fibrosing stage in which the patient developed chronic renal failure and died. This condition was accepted as being of post-streptococcal nature. Type II glomerulonephritis was a completely different disease, in which the patient presented with a slowly developing nephrotic syndrome; this eventually progressed to chronic renal failure in the majority of cases, although in a few complete recovery ensued. The pathology of this second type, according to Ellis, was basically a thickening of the glomerular capillary walls, although other complicating and often inflammatory features were described in some cases. The cause of the capillary wall thickening was quite unknown, and likewise the aetiology was obscure. It must be appreciated that all the histological material on which this extremely perspective concept was based was post-mortem in nature.

The more complex and subtle types of glomerulonephritis were at that time almost unrecognised. Most cases of glomerular disease were put into one or other of the two main categories if no generalised systemic condition such as diabetes mellitus was present. Focal glomerulonephritis was not well appreciated as a clinical or pathological entity, and

the existence of a functional disease of the glomerular capillary basement membrane unassociated with gross structural glomerular changes was unsuspected. It was at this historical point, in the middle 1950's, that the electron microscope became functionally translated from anatomy to the pathological field, and began to answer some of the questions which light microscopy had created but had been unable to solve; and it was at approximately the same time that renal biopsy became practical, safe and an accepted part of investigation of renal disease.

## *"ELLIS TYPE II" GLOMERULONEPHRITIS*

### REAPPRAISAL OF CLASSIFICATION

The first real impact of electron microscopy on human renal disease was in the field of what was then known as Ellis Type II glomerulonephritis. It was becoming obvious that Ellis had, in fact, included in this group a number of different conditions, some of which were basically inflammatory; many cases which clinically could be placed in this group showed histological features which were in fact those of Type I glomerulonephritis, with the addition of some glomerular capillary wall thickening and focal hyalinisation of the tufts. The development of such progressive cases of acute glomerulonephritis could now be followed by means of serial renal biopsy.

In addition, increasing knowledge of the effect on the kidneys of some systemic diseases of the so-called "collagen disease" group, for example, disseminated lupus erythematosus, had revealed that clinical states ranging from acute glomerulonephritis to a pure nephrotic syndrome could be produced by these conditions, and a corresponding variety of histological features was possible, including glomerular capillary wall thickening.

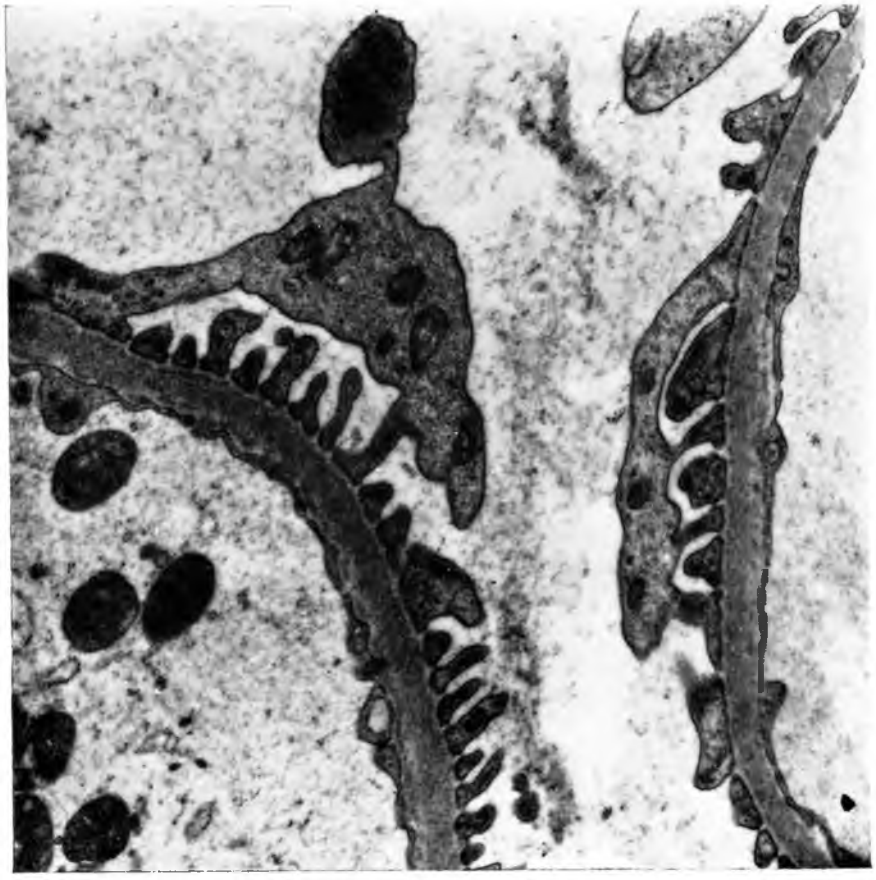


*Fig. 1.* This figure shows part of a normal human glomerulus; two capillary walls are seen, and the epithelial pedicel structure is well demonstrated. x 15,000

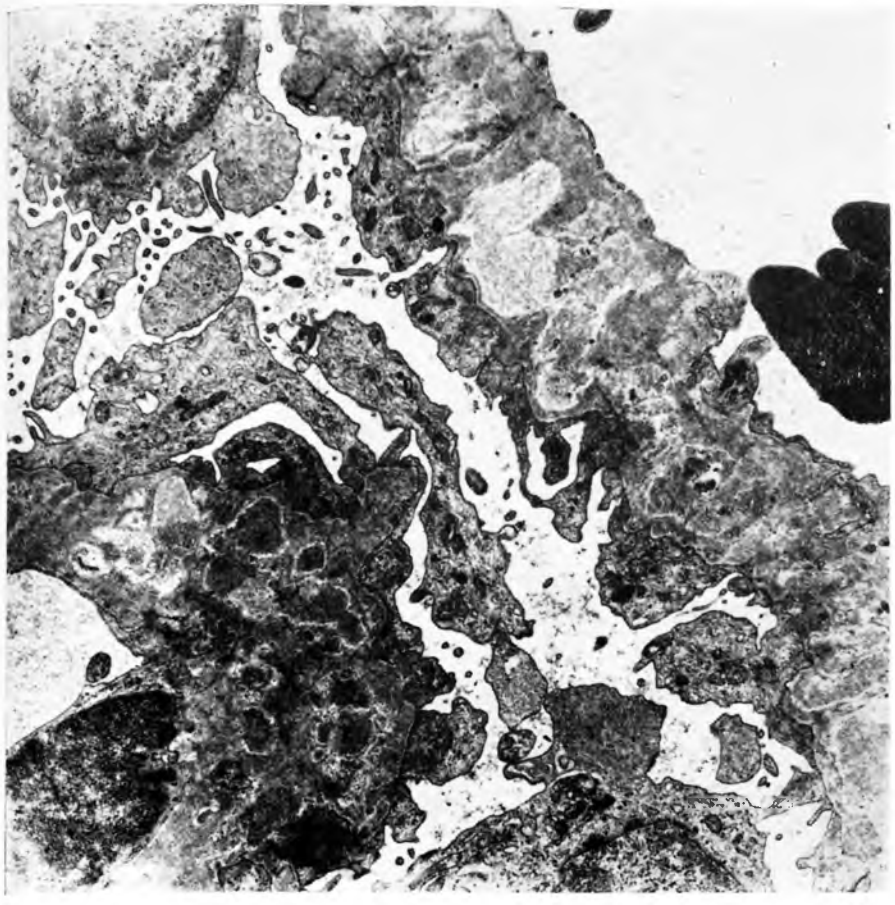


*Fig. 2.* This micrograph is from a case of membraneous glomerulonephritis. Two glomerular capillary walls are seen, and it is obvious that their structure is quite abnormal. Vacuoles are present in the basement membrane, which is thickened and irregular, and some dense, granular deposits are also visible in this layer. The epithelial layer is continuous over the basement membrane. x 8,000

As a result of these advances, it became obvious that when all cases which could be placed in other categories were removed, the group of patients with Type II glomerulonephritis consisted of individuals exhibiting clinically a pure nephrotic syndrome and showing on renal biopsy no inflammatory or proliferative changes of any significance in the glomeruli. Specimens from these patients showed either a diffuse thickening of the glomerular capillary walls, or, surprisingly, no glomerular abnormality of any importance. It became clear that the development of the former lesion was towards increasing capillary wall thickening and obliteration of normal glomerular structure, with glomerular ischaemia and progressive renal failure. It is perhaps natural that at this time the type of case in which no capillary wall thickening or other glomerular lesion was evident was thought to be simply an early stage of the condition, and that given time it would progress to a stage at which the capillary wall thickening became visible on light microscopy.

## PATHOLOGICAL CHANGES

Electron microscopic investigation of these cases, by this time usually referred to collectively as early and late stages of Type II glomerulonephritis, now began to throw light on the structural changes involved and on the relationship of the conditions, changing completely some of the ideas hitherto accepted without question. The hyaline thickening of the capillary walls seen in the so-called late stage of the condition was found to be accounted for by a complicated change in the structure of the capillary walls and in the relationship of their three main components. (Fig. 2). The basement membrane itself, which, as will be recalled, is the middle layer of the capillary

wall, had become of irregular thickness, and often much thicker than normal: very dark patches or deposits were visible between it and the epithelium, and the latter had completely lost its pedicel structure, lying in a continuous layer over the uneven basement membrane. The endothelium was often thickened, and the cells occasionally showed evidence of slight proliferation. Vacuoles tended to appear in the basement membrane, and in later cases the capillary walls could be seen to be composed of a confused mass of basement membrane material and fragments of epithelial or endothelial cytoplasm, with little or no evidence of the original three distinct layers. Such changes, or modifications of them, were always seen in cases in whom the renal biopsy had shown glomerular capillary wall thickening by light microscopy.

In the other "early" group of cases, that is, these patients in whom renal biopsy on light microscopy had revealed no significant change in glomerular structure, electron microscopy showed that the basement membrane was apparently normal in thickness and composition, but that again the epithelial cells had lost their pedicel structure, and the epithelium lay in an almost continuous layer over the basement membrane. (Fig. 3). As in the group of cases previously described, the endothelial cells sometimes showed a little proliferation.

Recalling that this latter type of case was thought to be an early stage of the condition, and that the fully developed state involved marked basement membrane changes visible on the electron microscope, it will be understood why the two types of cases were now referred to as early and late stages of *membranous glomerulonephritis*. It was considered, both from the structural and functional points of view, that in this disease, involving as it did proteinuria as its main feature, the glomerular capillary basement membrane must be the site of the basic lesion. The position of the epithelial cell changes in the aetiology was not well understood, but it was felt that the loss

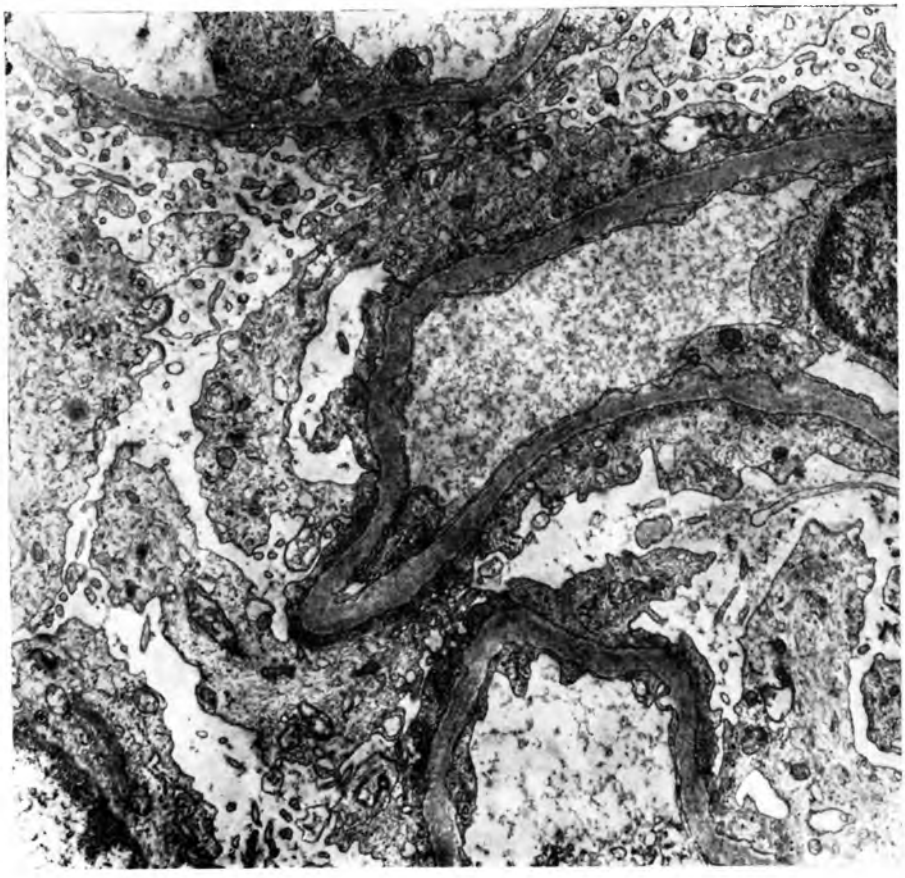


*Fig. 3.* This shows part of a glomerulus in a case of minimal lesion glomerulonephritis. The basement membrane of the capillaries appears normal, but the epithelium has lost its pedicel structure, and lies in a continuous layer over the basement membrane. x 6,000

of pedicel structure might be in fact secondary to the proteinuria, constituting an attempt to "seal off" the points of leakage in the basement membrane.

### MEMBRANEOUS AND MINIMAL LESION GLOMERULONEPHRITIS

However, this relatively simple concept of membraneous glomerulonephritis was then undermined by a fact which became apparent only as the years went by, and more patients were followed up both clinically and by biopsy examination. The obvious corollary to the idea that there were histologically distinguishable early and late stages of membraneous glomerulonephritis would be the recognition of the transition of patients from one stage to the other, and up to the present this has simply not been proved to occur. In addition, patients in the so-called early stage are found to have proteinuria and oedema as severe as those in the "late stage". Patients suffering from the type of disease in which no glomerular abnormalities are visible on light microscopy may continue for a long time excreting protein and yet the light microscopy appearances of the glomerular capillaries do not become those of the "late stage", and in fact change very little, if at all. Likewise these patients have a good prognosis clinically, and while it is not possible to dogmatise on this subject, it appears that they do not progress to renal failure and hypertension as do the patients who exhibit histologically the more severe lesion. These findings cast grave doubt upon the advisability of regarding the two types of case as different stages of the same condition, and the idea has gradually evolved that they might be, in fact, two different diseases. The term "membraneous glomerulonephritis" has naturally been reserved for the type in which the capillary basement membrane is visibly abnormal, and the somewhat awkward name "minimal lesion glomerulonephritis" was coined for the condition in which glomerular capillary wall thickening is not visible on light microscopy. These terms are now well established as the nomenclature for the two conditions, and more and more clinical workers are apprehending the distinction between the diseases, and are appreciating the fact that the prognosis in minimal lesion glomerulonephritis is good, whereas that in membraneous glomerulonephritis is bad, although the disease may be of long duration.

### THE ROLE OF STEROID THERAPY

The common method of dealing with cases of both minimal lesion and membraneous glomerulonephritis is therapy by steroids. It would therefore be a matter of great difficulty to collect and compare series of cases of the two conditions in which repeated renal biopsy had been performed and in which the course of the disease had not been influenced by steroids. In fact, the majority of reports, relating to the investigation of such cases by electron microscopy in recent years, have referred to patients who had been given steroids at some time. It does seem probable, from observation of occasional untreated cases, that the natural history and microscopic appearances in membraneous glomerulonephritis are in general the same, whether or not steroids have been given: while there is an impression that such treatment may slow up the process, the light and electron microscopic appearances undoubtedly still show a continuous, although in some cases very slow, progression towards disruption of the normal structure of the capillary walls, with thickening and eventual obliteration of capillary lumina.

In minimal lesion glomerulonephritis, on the other hand, it is obvious that while some patients show spontaneous recovery without the aid of steroid therapy, in many individuals proteinuria will continue unless steroids are given, and will then cease, often within a very short time. Indeed, some patients can be shown to be highly sensitive to steroids, the proteinuria appearing and stopping as these drugs are withdrawn and reintroduced. The interesting fact in this connection is that in most cases electron microscopic investigation of the glomeruli, at a time when the patient has no proteinuria due to steroid therapy or to spontaneous cure, shows more or less complete restoration to normal of the capillary wall ultrastructure, with re-appearance of pedicels.

Basically a more important point, however, arising from the widespread use of steroid therapy, is the possibility that it could be this form of treatment which prevents cases of minimal lesion glomerulonephritis from progressing to membraneous glomerulonephritis. Without going into any detail, it may be said that there is a significant amount of evidence militating against this concept.

The actiology of minimal lesion and membraneous glomerulonephritis is quite obscure up to the present time, and indeed there is

no real evidence that they are the result of the same cause, or even related causes. As might be supposed, it has been suggested that the lesion is basically an immune reaction, possibly of "auto-immune" type : there is some positive evidence that this is so. However, no definite concept of the aetiology of these conditions has yet been evolved.

## *"ELLIS TYPE I" GLOMERULONEPHRITIS*

When we turn to the condition which Ellis described as Type I glomerulonephritis, and which was, in his view, a hypersensitive reaction of the glomeruli to the streptococcus, we find that here the electron microscope itself has made a less basic and categorical contribution : however, it is true to say that the advent of renal biopsy, with a combination of light and electron microscopic analysis, has transformed our appreciation of the significance of pathological glomerular changes in this condition, or rather, as soon became obvious, this group of conditions.

The essential lesion in what was then called Type I glomerulonephritis was a generalised proliferation of the endothelial cells of the glomerular capillaries with endothelial swelling, and consequent partial or complete blockage of the capillary lumina. This led to glomerular ischaemia, to which is due many of the important clinical features of the disease. This endothelial cell change is responsible for the fact that the name now usually given to this condition is *proliferative glomerulonephritis*. It was realised that many cases of this type of glomerulonephritis recovered completely, and that a few cases continued or recurred, developing in a clinically subacute fashion to a condition of hypertension and chronic renal failure, which always proved fatal. It must be appreciated once again that virtually all the pathological material available for examination in this respect was post-mortem in nature.

### PATHOLOGICAL CHANGES

When it became possible to visualise the changes going on in the kidney during life, some important and hitherto unrecognised points were discovered, and a much more complex classification began to evolve. In the first place, it was found that in renal biopsies from patients who presented with one or more of the clinical features of an acute inflammatory glomerular lesion, the lesions encountered were very varied. Some cases might show the characteristic, obvious endothelial cell proliferation with perhaps polymorph infiltration of the glomeruli : others showed only a very slight degree of this lesion, and in several cases the endothelial cell proliferation was very focal, occurring only in some glomeruli, and only in parts of these glomeruli. In addition, some biopsies showed small, scattered foci of necrosis in glomeruli; in other cases, endothelial cell proliferation was associated with localised thickening of the capillary walls, and occasionally this thickening had a bright, hypereosinophilic, refractile appearance. Other, more subtle characteristics were picked up as more series of biopsies were examined, and gradually composite pathological pictures began to be associated with certain clinical conditions. There is no doubt that we are yet far from a complete and satisfactory classification of the acute inflammatory lesions of the renal glomeruli, but we now possess an overall understanding of clinico-pathological correlation which is much greater than anything we have known before.

### CLASSIFICATION

In general, proliferative glomerulonephritis can now be divided into *diffuse and focal* types. Many of the cases of the *diffuse type*, in which virtually all of the glomerular tissue is involved, are obviously post-streptococcal in nature from a clinical point of view, and present the usual clinical features of this condition. Other patients, however, exhibiting similar histological features on renal biopsy, are not clinically diagnosable as definite cases of the post-streptococcal syndrome. In this situation, electron microscopy appears to offer some help. Examination of biopsy material by this means in several centres has suggested that in true post-streptococcal cases, a characteristic feature can be found in the glomerular capillaries when the disease has been present for some time. This consists of a few, scattered, large, localised granular deposits of darkly osmiophilic material lying on the epithelial surface of the basement membrane, pushing deeply into the epithelium which has often lost its pedicel structure in this region. Whether this feature will be found to be sufficiently pathognomonic to be used as a parameter for diagnosis of post-streptococcal disease remains to be seen.

*Focal glomerulonephritis* has become a fairly common diagnosis in renal biopsy material;

patients exhibiting this pathological condition may present with a variety of clinical features including haematuria, proteinuria, oedema, hypertension. The focal lesions in the glomeruli may be simply of endothelial cell proliferation, or may include small patches of necrosis or focal capillary wall thickening. Some of these cases are found on examination to be quite definite, but mild, cases of post-streptococcal glomerulonephritis; but many others turn out to be in fact cases of so-called "collagen disease" of some type, usually disseminated lupus erythematosus or polyarteritis; Henoch-Schönlein disease also can be associated with such a histological picture. While in many cases electron microscopy is not able to distinguish between these conditions, a diagnosis of disseminated lupus erythematosus may be strongly supported by the finding of thin, dark, layered patches of a finely granular material, lying between the glomerular capillary basement membrane and the endothelium; this feature is very frequently seen in proved cases of the condition. Such supportive evidence for the presence of disseminated lupus erythematosus may be of great help in dealing with a case otherwise difficult to diagnose.

## CONCLUSION

There is no doubt that we are still only scratching at the surface of the problem of glomerulonephritis, in spite of the very numerous specialised techniques now being used in its investigation. The cause of minimal lesion and membraneous glomerulonephritis, the complex question of the reaction of the glomerulus to the streptococcus, the reasons for the varying types of development of cases of acute proliferative glomerulonephritis, the problem of proteinuria in the presence of a basement membrane normal to ultrastructural examination — all these, and many more difficulties, must be elucidated before we can claim to have a rational insight into the diseases which affect the glomerulus, and before we can evolve a really intelligent mode of therapy for these conditions.

## FURTHER READING


1. Ciba Foundation Symposium on Renal Biopsy: 1961: Edited by G. E. W. Wolstenholme and M. P. Cameron. Publishers, J. & A. Churchill, London.
2. Electron Microscopy of the Kidney in the Nephrotic Syndrome: MacDonald, M. K., and Ruckley, V. A., Proc. Roy. Soc. Med.: Vol. 59: 1966: p.515-518.
3. The Nephrotic Syndrome: J. S. Robson. In "Renal Disease", Chapter 11, edited by D.A.K. Black, Published by Blackwell Scientific Publications, Oxford, 2nd Edition, 1967 (in press).


## ACKNOWLEDGEMENTS


The author wishes to acknowledge the help of Dr. V. A. Ruckley, who is responsible for much of the electron microscopic work upon which this article is based. Dr. Ruckley is a Medical Research Council Fellow. Equipment has been provided by generous grants from the Advisory Committee on Medical Research and from the Lawson Tait Memorial Trust.


---

## EXPERIENCE

"Our own Experience is but a narrow field to walking. Man's life is short, nor is even that little spent in Medicinal Enquiries, so that it is a pity so useful a part of knowledge should have no wider Bounds; but even limited as it is we tread surer when we rely on it than trust to the Experience of others. What a man has himself seen he is much more certain of than what he is told by others; the pleasure which the success or the pain which a disappointment may have given him, strike him more deeply, and make him for the future more bold or more cautious as his case requires."

(Extract from one of the earliest Dissertations in the library, dated 1751.)

# THE STRUCTURE AND FUNCTION OF IMMUNOGLOBULINS IN MAN

J. A. HABESHAW, B.Sc., M.B., Ch.B.

## INTRODUCTION TO PART I — STRUCTURE

The cells of the blood, and their supporting fluid are among the most extensively studied biological systems. It is with the fluid portion of the blood that this article is concerned and with a small group of proteins in particular, the immunoglobulins. These show a peculiar and unique behaviour in the presence of other substances called antigens. This behaviour may take the form of combination forming an insoluble precipitate (precipitin reaction), or rendering it more easily phagocytosed by the microphages or macrophages (opsonisation). Other reactions between antibody globulin and antigen are complement fixation in which the four components of complement take part, immune adherence between antigen and adsorbed antibody, and sensitivity reactions such as passive cutaneous anaphylaxis and the Prausnitz-Kustner reaction. However, the central feature of immune reactions is that antibody by definition can only be identified by its reaction with antigen. Identifiable antibody forms only a small part of the total globulin fraction of serum. The remaining globulin may be physically indistinguishable from antibody, but lacks its demonstrably specific activity; this has resulted in the term "Immunoglobulin" being substituted for "antibody" in this article whenever this sense is intended. The greatest barrier to the understanding of the nature of immunoglobulins is the classification used to describe them. This classification has been imposed by the technical procedures necessary for the isolation and identification of these proteins. Thus an understanding of these methods is a necessary requirement and is dealt with in the first part of this article. The classification and the physical, molecular and chemical structure of immunoglobulins are also discussed.

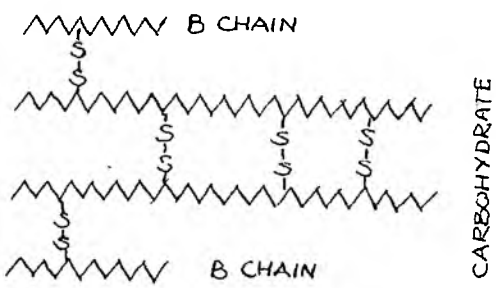
## METHODS OF STUDY

Globulins may be separated from the other serum proteins by selective precipitation with saturated ammonium chloride solution or with ethanol at low temperatures; methods which yield a relatively crude protein fraction of low solubility. If immune serum is treated in this manner, most of the antibody activity is found to remain in the reconstituted precipitate. The globulins themselves are a heterogenous group of proteins differing widely in terms of molecular size and chemical composition. Crude "salting down" yields little information as to the physical properties of any antibody, other than its behaviour as a globulin.

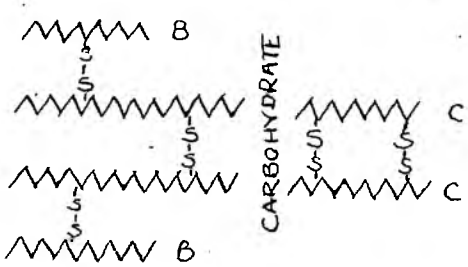
Globulins may be separated into three main classes by a process known as electrophoresis. This principle employs the movement of proteins in an electric field at constant pH; the rate of migration towards the cathode being proportional to the excess ionic charge each molecule carries, and to its size and behaviour in the suspending medium. By this method, three broad classes of globulin emerge, called alpha, beta and gamma, the latter being the slowest moving at a pH of 8.6 in agar gel. It is among the gamma globulins that antibody activity is found. Further electrophoresis under different conditions of pH and potential difference will separate the slow moving gamma globulins into two further groups termed gamma 1 and gamma 2. The former migrate in a band close to the beta globulins, and have therefore, in some classifications, been termed $beta_2$ globulins.

Again electrophoretic separation tells comparatively little about the fine physical struc-

ture, the size, or the shape of the immunoglobulin molecule. These characteristics may be studied by ultracentrifugation. In the ultracentrifuge, the heavier molecules separate first, and lighter fractions later. The behaviour of these molecules is measured in Svedburg units, a measurement derived from a modification of Stoke's Law. The heavier molecules are termed 19S in terms of sedimentation characteristics and the lighter ones 7S. Antigen combines with one or other of these fractions of gamma globulin, more usually with the 7S fraction which is also the greatest in bulk. By these methods, a complete separation of gamma globulin is possible into reproducible fractions. The different behaviour of these fractions must be determined by more sophisticated immunological and physical techniques which are beyond the scope of this article; the scheme below is sufficient for its purpose.




4 CHAIN STRUCTURE




6 CHAIN STRUCTURE

AFTER S. COHEN & R.R. PORTER 1964

The gamma$_2$ Globulins are a homogenous group of proteins upon ultracentrifugation, while the gamma$_1$ globulin may be separated into components with both 7S and 19S characteristics. In this group also small fractions with intermediate sedimentation rates emerge, although to the lighter end of the scale.

#### CLASSIFICATION

Employing the methods described, three types of immunoglobulin may be distinguished. They are classified as follows:—

(1) The gamma$_1$ globulins with sedimentation characteristics of 19S, and belonging to the group with fast motility upon electrophoresis ($\beta_2$ globulins). They are also called "macroglobulins". Equivalent terms for this group are $\alpha_1$M; $\beta_2$M; or IgM.

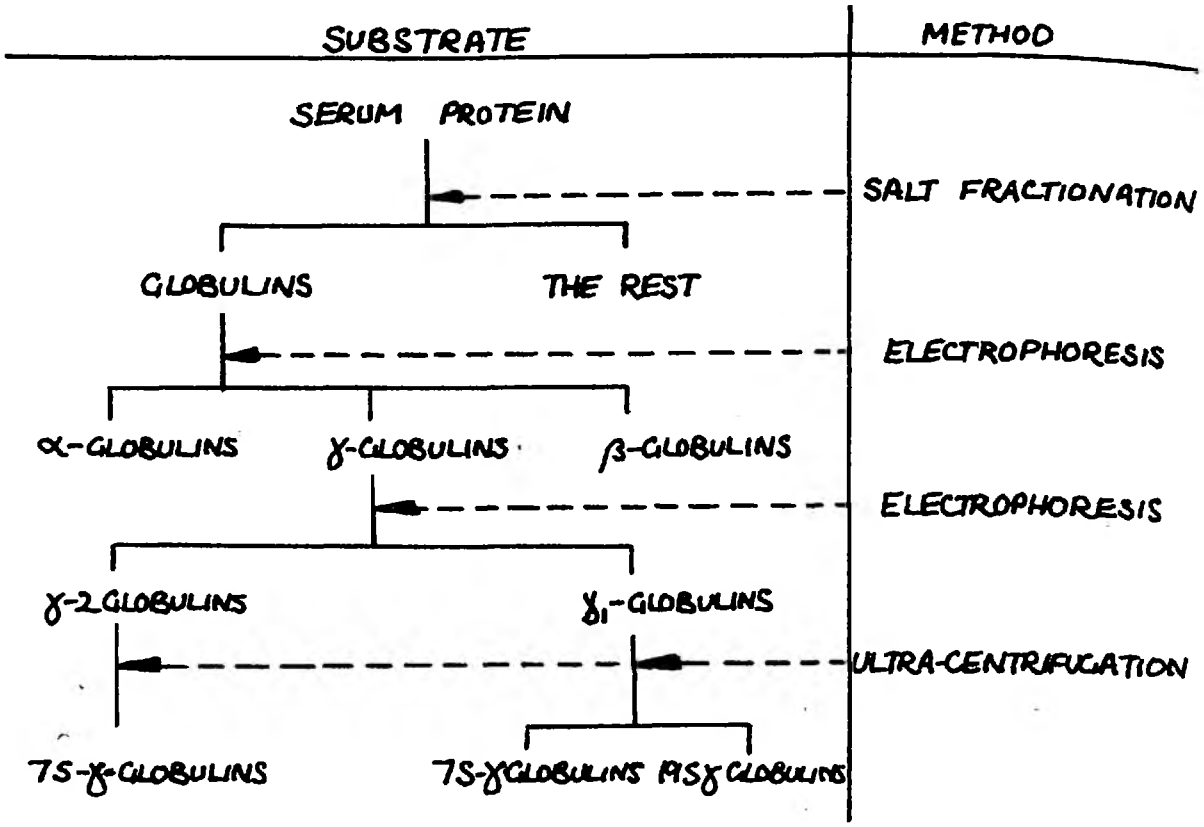
(2) The remainder of the fast gamma group with sedimentation characteristics of 7S. These are also called $\alpha_1$A; $\beta_2$A; or IgA.

(3) The gamma$_2$ globulins which all sediment at 7S. These are termed also $\alpha_2$A; or IgG.

Gamma globulins may also be identified by the cells producing them; and by their immunological reactivity, although they cannot be usefully classified by these means. For example, reaginic antibodies or "reagins" are classified as those antibodies spontaneously produced in susceptible individuals which produce skin sensitisation. This kind of classification is one which make use solely of the immunological reactivity of the antibodies studied. Other classes of antibody might be called "Opsonins" or "Precipitins" but fundamentally such appellation is misleading since precipitating antibodies may be opsonising under certain conditions. Even more significantly, the class of opsonising antibody is indistinguishable from the class of precipitating antibody by the physical characteristics displayed on electrophoresis or ultracentrifugation. Fortunately, the reaginic antibodies, which are the most difficult to study immunologically, in general show the physical characteristics of the IgA group of immunoglobulins. To date it appears that the most satisfactory way of classifying immunoglobulins is by their physical rather than immunological behaviour. Each class of immunoglobulin classified by such means has several important members, both naturally occurring and pathological.

#### PHYSICAL STRUCTURES

The structure of immunoglobulins has lately




become the subject of close scrutiny, firstly by reason of investigating the synthesis of highly specific proteins by the cell, such as enzymes and hormones, and secondly because antibodies are thought to provide a unique example of an "adaptive" alteration in the synthetic mechanisms of the cell. Students of the structure of immunoglobulins hope to discover the answers to both these questions in the scrutiny of the physical, molecular, and chemical structure of these proteins.

Of the immunoglobulin content of human serum IgG (gamma$_2$ A) globulin forms 80-90%, Igm (gamma$_1$ M) 5-8%, and IgA somewhat less than 2% of the total.

The molecular weights of IgG and IgA are somewhat similar, being in the order of 150,000 to 190,000. The macroglobulin, on the other hand, has a molecular weight of 1,000,000 and in some diseases abnormal macroglobulins with twice this molecular weight have been reported.

These molecules also differ in their shape. The molecule of IgG is found to be elliptical, with a ratio of long:short axis of 8-9:1, and a maximum dimension of some 70Å. The molecule of IgM is almost spherical in shape with a diameter of at least 3000A. Since different observers have recorded similar dimensions and molecular weights under varying experimental conditions we may assume their true dimensions to lie within this range.

#### MOLECULAR STRUCTURE

The reactive site of an antibody molecule is relatively small, since reactive fragments of low molecular weight can be discovered after fragmentation of the molecule. Such treatment also reveals that each antibody molecule can be split into four or six primary fragments by the hydrolysis of disulphide bonds. These fragments are called A, B or C chains, and are made up of amino acids linked in polymeric form. Further study has shown the B chain fragments of any human immunoglobulin to be similar to the B chain fragments of any other, while the A chains are distinct in each of the three classes. It is also clear that the specificity of antibody is due more to the sequence of amino acids in each B chain, than to the tertiary structure. Despite this, NO clear concept relating structure to biological activity has been suggested. For interest, the two theoretical structure diagrams of immunoglobulin molecules are given.

### CHEMICAL STRUCTURES

All three major classes of immunoglobulin contain carbohydrate, and this is true of all species studied, including man. The macroglobulins contain five times as much carbohydrate as the IgA and IgG globulins, amounting to 12%-15% of the total dry weight of the protein. Although clearly an important part of the molecule, antibody fragments free of carbohydrate may still react with antigen. The carbohydrate is retained almost entirely on the A chain after enzymic splitting. The small portion associated with the B chain may also be a functionally important part of the molecule. The carbohydrate is always composed of a combination of the following sugar groups known as hexose, fucose, hexosamine or sialic acid.

It might be expected that different antibodies produced in the same animal would show differences in amino-acid composition; but the results obtained from such studies have been disappointing. This might indicate that the antibody combining site is a small part of the molecule. Obviously the secret of antibody specificity resides in the sequence of amino acids rather than in the preponderance of one or other reactive group. Yet differences detectable by amino acid analysis do exist between one antibody and another, although they are slight compared with the more obvious differences between immunoglobulins and other classes of protein. The characteristic features of immunoglobulin are their content of hydroxy and dicarboxylic amino acids, especially proline.

Although differences between individual immunoglobulins are difficult to detect, similarities are more easily demonstrated. Antisera prepared to the human immunoglobulins IgA, IgG and IgM all cross react. This indicates some basic structural similarity between different types of globulin; indeed except for the antibody combining sites, the B chain fragment of any immunoglobulin is similar to that of any other on immunological testing, while the A chains appear to be distinct in each of the three classes.

### INTRODUCTION TO PART II — FUNCTION

An antibody response is found in primitive vertebrates such as the lamprey (Petromyzon) and in all later evolutionary phyla. As shown by comparative embryological studies, the ontogenic development of anatomical structures, such as the pharyngeal pouches is paralleled in the ontogenic development of lymphoid tissue and synthesis of antibodies. In primitive vertebrates, all the antibody formed is macroglobulin of the 19S type, while in mammals the bulk of it is 7S globulin. The production of antibodies in the neonate parallels the phylogenic development of the antibody response. Initially unresponsive, the foetus first acquires the ability to reject homologous tissue. Then it acquires, in late intra-uterine life, the ability to produce 19S macroglobulin in response to appropriate stimulation. Not until some months after birth does the capacity to produce IgA or IgG develop. This chage in the production of IgG in preference to IgM in the mammalian phyla, is recapped in the transition from primary to secondary response at any stage of life. In the primary response, macroglobulin is produced, to be superseded by IgG as the secondary response develops. Thus, in early neonatal and late intra-uterine life, the mammal appears to repeat those evolutionary changes from Lamprey to mammal in respect of antibody synthesis. It would appear obvious that the synthesis of immunoglobulin is necessary for the life of both vertebrates of primitive type, and mammals. It has been assumed that the rôle of the immunoglobulins is the protection against infection. But in the amphibia, for example, the secretion of antibodies is slow, and their protective effects negligible. Such reasoning leads to reflection upon the actual nature of the antibody reaction — is the secretion of antibody an end, or is it merely the serological reflection of some fundamental change occurring within the cell? The second half of this article will attempt to answer this question by examining the rôle of immunoglobulin as a defence mechanism, as a metabolic intermediary, as part of an integrated system of immunity and metabolism, and finally as a theoretical postulate.

### AS A DEFENCE SYSTEM

Following the injection of antigen into an animal, specific antibodies begin to appear among the immuno-globulins of the serum. If a primary response occurs, the specific antibodies are of the macroglobulin type, and occur in low titre. These are soon replaced by the appearance of IgG, and any subsequent challenge by antigen evokes the same IgG response. A few antigens evoke a biphasic response, in which IgM and IgG both persist together; an example of this is the tubercle bacillus. The antibodies secreted combat the infection which stimulates their production in

several ways. Firstly they tend to render the organisms more liable to phagocytosis and ultimate destruction within the macrophages of liver, spleen and lymph nodes. Secondly, antibodies immobilise bacteria by a process known as immune adherence, whereby the organisms are bound to cells which have adsorbed the specific antibody, and thirdly, the antibodies in conjunction with complement may bring about lysis of the bacteria. However, by themselves the immunoglobulins are relatively ineffective inhibitors of bacterial multiplication. In most cases the lethal agent is the cell which phagocytoses the bacterium. Yet the presence of antibodies to a certain organism may exert a protective effect, and the extent to which they do this depends upon:—

(a) the type of antibody present, and its concentration
(b) the virulence of the organism and its type
(c) the time interval between the primary challenge which evoked the antibodies and the secondary challenge.

In the initial primary response, the antibody formed is macroglobulin, and it is present in low concentration. Its protective effects are not as great as those of the 7S gamma globulin which supersedes it. Organisms of high virulence, such as the meningococcus, and salmonella typhi although very susceptible to the effects of antibody may overwhelm the host before sufficient antibody can be produced. In the secondary response, the antibody is 7S gamma globulin, present in high titre, and rapidly produced. As a consequence even virulent organisms are quickly eliminated. It is this type of antibody which confers immunity of the classical descriptions and which must be accorded a central rôle in defence.

Certain types of organism are susceptible to attacks by antibody. Among the bacteria, the pneumococcus, meningococcus, and salmonellae must be mentioned. Viruses are among the most susceptible of all organisms, and the presence of specific antibody inhibits the viraemic phase of most infections with virus. Paradoxically, the life-long immunity conferred upon an individual by an attack of mumps or measles, is not due to humoral antibody, which becomes undetectable in a relatively short time, but to an alteration in susceptible cells which renders them immune to virus attack.

In infections with protozoa, or metazoan parasites such as cestodes or nematodes, the antibody formed appears to modify the course of the infection but slightly, often because of the situation of these parasites.

The duration of the primary, or macroglobulin response is from 5 days to three weeks. The secondary response to a single dose of antigen may produce blood levels which remain detectable from months to years, depending on the type of antigen. The duration of this secondary response is related to the persistence of antigen; pneumococcal polysaccharide may persist in mice for up to 200 days after a single injection. Furthermore, small, almost undetectable, amounts of antigen may persist for very long periods within the cells, and adsorbed onto reticulin fibres within the spleen and lymph nodes. A detectable secondary response will occur within 2 days of the injection of antigen if the primary challenge has occurred within 2 to 3 weeks prior to the secondary challenge. As a general rule, the longer the interval between two injections of antigen the more sluggish is the secondary response. In foetal, neonatal and germfree animals, no secondary response appears to occur; the antibody formed being always macroglobulin unless adjuvants or very high doses of antigen are used.

#### METABOLIC AND REGULATORY FUNCTIONS

It was not until very recently that some proof of a direct intervention of immunoglobulin in the regulatory mechanisms of the body was discovered. In thyrotoxic patients, the substance, Long Acting Thyroid Stimulating hormone (L.A.T.S.) was shown to be a specific 7S immunoglobulin, which fixed to microsomal fractions of thyroid cells. The bulk of the immunoglobulins, as stated earlier, have no demonstrable antimicrobial activity. Indeed, since the antibiotics were introduced, many patients with very low immunoglobulin levels have been recorded; they suffer from the condition of hypogammaglobulinaemia. Despite this relative lack of immunoglobulins many of these patients survive for ten or twenty years. On closer analysis, NO case has been found in which immunoglobulins are entirely absent, and it may be concluded that a complete absence of the immunoglobulins is incompatible with life. Thus the immunoglobulins may be depressed without hazard providing infections are controlled, yet their complete absence has never been recorded. By analogy with the discovery of L.A.T.S. the small fraction of immunoglobulin necessary for life may serve to regulate the external or internal secretions of glandular tissues. Indirect

evidence of such activity may be inferred from studies of the "auto-immune" diseases of thyroid, pancreas, salivary gland, stomach and adrenal, where hypofunction is frequently associated with specific immunoglobulins directed towards microsomal fractions of these tissues. It could be postulated that immunoglobulins are to some extent merely another aspect of the fine feedback mechanisms controlling the functions of glandular tissues.

An essential part of the integrity of function of the body is the ability to repair and replace dead or damaged tissues with either new cells or scar tissue. After trauma resulting in massive cell death, changes can be detected in both the immunoglobulins, and the alpha II fractions of serum proteins. An increase in both these fractions occurs in response to tissue injury; that of the immunoglobulins may result in the facilitation of removal of dead tissue by opsonisation, and the alpha 2 globulins are increased whenever rapid tissue growth occurs. In haemolytic anaemias, the presence of antibodies to red cells shortens their survival time; in the post-irradiation regeneration of bone marrow the alpha 2 globulins are increased. Therefore, a balance of these two factors might be expected to result in controlled regeneration of damaged tissue.

### THE ROLE OF IMMUNOGLOBULIN IN AN INTEGRATED SYSTEM

As far as is known, immunoglobulins are secreted only by the lymphoreticular system, which for present purposes may be regarded as a trio composed of the macrophage, the lymphocyte, and the plasma cell. The immunoglobulins in the serum mirror the changes of cellular pattern in the lymphoreticular system in subtle and fascinating manner. Thus an increase in macroglobulin means hyperplasia in the large lymphocyte element of the R.E.S.; increase in IgG means hyperplasia of the plasma cell. Neither cell type is capable of producing specific immunoglobulin in the absence of the macrophage, which removes bacteria and damaged tissue wherever they occur. The most recent considerations of antibody formation suggest that the macrophage passes on a substance, possibly R.N.A., to the large lymphocyte prior to the secretion of macroglobulin antibody. In the secondary response, the macrophage may not be the initiating cell. The rôles accorded to the different types of immunoglobulin can be reconciled with their cellular origins, and the immunoglobulin can be reconciled with their cellular origins, and the immunological status of the organism. In the foetus, the only antibody present appears to be of maternal origin. This crosses the placenta in selective manner; only 7S gamma globulin will pass, macroglobulins are excluded as are 7S antibodies of reaginic type. Yet when the neonate forms immunoglobulin it forms macroglobulin, the first antibodies to appear being the blood group substances. Thus the macroglobulins might be termed "identity proteins", and the 7S immunoglobulins "immunity proteins". In the primary response macroglobulin is secreted, following which the "identity" of the animal becomes more or less permanently changed, since any further challenge with the same antigen evokes a secondary response. This indicates some cellular change of a permanent nature by at least some cells. Animals in a germ-free environment will synthesise only macroglobulins, even when a fresh antigenic challenge is supplied, again suggesting an "identity" type of change in the organism, rather than an "immunity" one. The most frequent example of "identity" changes in an organism excluding primary infection, is probably tumour growth. The association of lymphoreticular hypoplasia with advanced tumour growth, cachexia, and immunological disturbance is evidence, admittedly diffuse, of some reaction to tumour growth which can scarcely be termed "immunological" in that sense. Moreover, "immunity" to transplantable tumours is only partial and no secondary response occurs.

In response to tissue injury, macroglobulins only are formed in non-pathological states, yet pathological states can be induced by causing the synthesis of 7S immunoglobulin with adjuvants. Here, the non-pathological "identity" change has been superseded by a pathological "immunity" one. The antibodies work with the macrophages to remove or neutralise all extraneous material with antigenic properties, whether this is "foreign" in the form of bacteria or viruses, or arises from the tissues of the organism itself. Their structure and their immunodynamic characteristics fit them for their respective rôles; the prompt synthesis and high combining power of the 7S immunoglobulins in combating bacterial invasion may be cited. The widespread distribution of the lymphoreticular tissues which produce the immunoglobulins also determines that local disturbances, however small, will be met with the appropriate response. The rôle of macroglobulin in this integrated system remains

enigmatic; some macroglobulins, called Milgrom factors, inactivate 7S gamma globulins, and also complement, and could thus act as a control upon the reactivity of the 7S antibodies.

#### THEORETICAL CONSIDERATIONS

In considering the functions of immunoglobulins, the realisation of the state of the tissues producing them is essential. The serum can never be considered in isolation; it is merely a reflection of the widespread changes in underlying cell systems. The functions of immunoglobulins as a system of defence, of metabolic significance, and as an integration system co-ordinating those functions termed "identity" with those termed "immunity", have been considered. Theoretically, the function of immunoglobulin may extend even beyond these considerations. Start with the assumption of Le Chatelier's principle that in a closed stable system any disturbance is met with a change in the physical state which tends to negate the initial disturbance and restore equilibrium. This results in the establishment of an oscillating system analogous to the damped simple harmonic motion familiar in physics. Many well defined examples of servomechanisms occur in biological systems, both at the cellular and organisational levels. The disturbances the whole organism is subject to may be regarded immunologically as affecting the integrity of the body, and the functions of the immunoglobulino-lymphoreticular system act to restore the equilibrium state.

The mechanisms employed, or theoretically able to be employed to these ends are, (a) Stimulating increase in function of some cells, (b) Removal of malfunctioning cells, (c) Inactivation of biologically active materials, such as hormones or enzymes, (d) Neutralisation of toxic materials, (e) A change in the balance between types of tissues; for example, the excess red cell mass occurring in people adapted to high altitudes, (f) Adaptive cellular changes. The immunoglobulins are the effector agents of the lymphoreticular tissues. They can, under certain conditions, increase the functions of cells; for example, the discovery of L.A.T.S. Their rôle in the removal of malfunctioning cells, and inactivation of biologically active materials may be regarded as probable, and neutralisation of toxic materials is achieved by the antibody — Kupffer cell — liver parenchymal cell relationship.

The last two considerations are problematical; but suffice it to say that a relationship can be established between the mass of lymphoid tissue and body mass. People with lymphopenia and hypogammaglobulinaemia, however induced, are always wasted: experimental examples of this are runting syndrome, and long term corticosteroid administration.

In the field of adaptive changes it is obvious that specialised cells, such as liver, kidney and brain, can only adapt within the context of genetically predetermined functional capacity. The lymphoreticular system can adapt in a more subtle way by altering permanently the types of immunoglobulins secreted, and their specificity. The white cells of a sensitised individual are permanently changed from their pre-sensitised state, thus ensuring that any subsequent challenge is met with a modified repsonse. This has been teleologically interpreted as "recognition" of self or not-self, but fundamentally it is merely the reactive state of the organism at the time of challenge before or after adaptive changes have taken place. An amputee fitted with a prosthesis regards it a "self" when walking with it, because he has adapted his form of locomotion to using it. Similarly, it is "not-self" when he removes it before bed because he has not adapted to sleeping with it. The ability to adapt not merely the cells of the R.E.S. but the cells of the whole of the body to the external environment occurs at and after birth. During this short period, the infant is without macroglobulin, as it is throughout the period of intrauterine life. This process, called "adaption" in this article, means the establishment of an initial state of equilibrium. Any antigen introduced during the initial neonatal period of refractivity becomes accepted and treated as self. It is incorporated into the immunological "body image". Subsequent challenge with the same antigen shows the animal to be tolerant to it: no antibodies are formed. To prevent pathological bacteria being incorporated into the "body image", the neonate is protected by transferred maternal 7S immunoglobulin. It is interesting to postulate that the symbiotic bacteria of the mouth and bowel are immunologically treated as "self" and it is because of this they owe their favoured position as symbiants. Germ-free animals remain in a state of foetal organisation in regard to intestinal tract and lymphoreticular system if deprived of these bacteria. They may indeed be the agents which provoke the synthesis of 7S immunoglobulins which marks the maturation of the lymphoreticular system. This

postulated theoretical proposition of the immuno-globulin-lymphoreticular tissue system shows how even the structure of immunoglobulins may be of importance in attempting to unravel the complexity of this most complex structure. The central point is the selective passage of 7S immunoglobulin across the placenta, while macroglobulin is adsorbed and fixed to the placental villi. If macroglobulins are indeed "identity" proteins, their presence in the placental villi might prevent the rejection of the placenta by the mother. Whatever the actual functions of the immunoglobulins prove eventually to be, it is certain that they have some part to play in the organisation and regulation of the growth of the tissues of the body.

#### PART III — SUMMARY

The methods used to classify immunoglobulin in respect of its physical and chemical structure are described. The rôle of immunoglobulin as a defence mechanism together with an analysis of its probable metabolic functions is discussed. The theoretical possibilities of the immunoglobulin and lymphoreticular system as both an integration system and an adaptive one are examined.

#### APOLOGY

In this article two parts may be distinguished, that which may be accounted fact forms the first part. The second is an admixture of fact and ideas, and on reflection it is by no means easy to distinguish one from the other. As an apology, allow this warning to be offered; this article is not a textbook, the ideas put forward may well be wrong. It was written as both an exercise and an amusement and should be read in the same spirit.

#### *REFERENCES — GENERAL*


1. Goodman, H.C. (1964). "Immunological Methods", a Symposium organised by the Council for International Organisations of Medical Science. Page 143. Edited by J. F. Ackroyd.
2. Suter, E., and Ramsvier, H. (1964). "Cellular Reactions in Infection", *Advanc. Immunol., 4,* 117. Academic Press.
3. Munoz, J. (1964). "Effect of Bacteria and Bacterial Products on Antibody Response", *Advanc. Immunol., 4,* 397. Academic Press.
4. McKenzie, J. M. (1965). "The gammaglobulin of Grave's Disease: stimulation by fraction and fragment", *Trans. Ass. Amer. Phycns., 78,* 174.
5. Stanworth, D. R. (1963). "Reaginic Antibodies", *Advanc. Immunol., 3,* 181.
6. Good, R. A., and Papermaster, B. W. (1961). "Ontogeny and Phylogeny of adaptive immunity", *Advanc. Immunol., 4,* 1.
7. Cohen, S., and Porter, R. R. (1964). "The structure and biological activity of Immunoglobulins", *Advanc. Immunol., 4,* 287. Academic Press.
8. Zweifach, B. W. (1960). "The contribution of the R.E.S. to the development of tolerance to experimental shock", *Ann. N.Y. Acad. Sci., 88,* Article I, 203.
9. Friedman, H. (1963). "The persistence of antigen in nucleoprotein fractions of mouse spleen cells during antibody formation", *Nature, 199,* 502.


---

## IS THAT SO?

"The warp of magnetic-fluid reaching between the person impregnated with such fluid, and the air-loom magnets to which it is prepared, which being a multiplicity of fine wires of fluid, forms the sympathy, streams of attraction, repulsion etc. as putting the different poles of the common magnet to objects operates; and by which sympathetic warp the assailed object is affected at pleasure: as by opening a vitrolic gaz valve he becomes agitated with the corrosion through all his frame, and so on in all their various modes of attacking the human body and mind, whether to actuate or render inactive . . ."

from "Illustrations of Madness"—with a description of the tortures experienced by bomb-bursting, lobster-cracking and lengthening the brain in the air loom. by John Haslam, 1810.

# THE SOCIETY

## RETROSPECT — THE 229th SESSION

At the time of going to press it can be said that we have just witnessed an historic session of Society business; a fundamental change in the atmosphere and conduct of Private Business has accompanied a new attitude to membership and a keen interest in the running of the Society.

There can be little doubt that the change was primarily wrought by our move from the dilapidated grandeur of Melbourne Place to the homely simplicity and warmth of Hill Square; and there is no doubt that livelier interest in the Society was sparked off and kindled by a most extraordinary Senior President, the flames being fanned further by a doughty Treasurer and Secretary.

One cannot but be impressed by the new potentialities of Private Business in the seminar-like atmosphere of Hill Square. The first session's business was perhaps a little shaky and experimental, but the liveliness, even the heated excitement, of many evenings has given great confidence to those who doubted the Society's chances of survival after the move. The Society has entered its first truly exciting phase for some considerable time.

Public Business, far from suffering, has gained a great deal in variety by its frequent changes of surroundings. The Society is most grateful to the Royal College of Surgeons and to the Post Graduate Medical Board for their unfailing generosity in providing accommodation.

With a new home there have inevitably come changes in the financial structure of the Society. In particular, the heating of Hill Square is both our strength and our downfall, for while it makes the libraries, museum and coffee lounge most popular places to work and meet in, its cost makes an almost intolerable burden on an already shaky current account. The equalising of pre-clinical with clinical subscriptions was thought both appropriate and fair to most members, and together with the increase in life membership subscription represented the first real increase in income since subscriptions were last increased, over fifty years ago. But although we were generously aided by the University Disbursement Fund we completed the session with more bills than could be met.

During the year we have been visited by a number of our senior members, and have been greatly impressed by the interest that they have taken in the new premises. A few of our private meetings have been attended by senior members of the profession, and we invite all life members and past presidents living around Edinburgh to come to both Public and Private Business, and to renew their active membership.

So we have completed our first year having doubled attendances at Private Business, and having created a Society with daily instead of weekly life. We look forward to the new session when we can build on this firm foundation.

R. H. SMITH, Scriba.

## SYLLABUS — SPRING TERM

Fri. Jan. 13—ADDRESS: Professor Neville Butler, M.D., F.R.C.P., D.C.H. "Pre-natal Paediatrics." *In Surgeons Hall, Nicolson Street.*

Fri. Jan. 20—Dissertation: Miss Clair E. M. Guthrie. "The Sacred Disease."

Fri. Jan. 27—TALK: Dr. George Ashcroft, M.B., Ch.B., M.R.C.P.

Fri. Feb. 3—Dissertation: M. H. Kaufman, Esq. "Foetal Distress."

Fri. Feb. 10—Dissertation: Ronald J. Nixon, Esq. "The History of Medicine in Malta."

Fri. Feb. 17—ADDRESS: Dr. Macdonald Critchley, C.B.E., M.D., F.R.C.P. "Some aspects of the Life and Death of Oscar Wilde." *In Surgeons' Hall, Nicolson Street.*

Fri. Feb. 24—Dissertation: Miss Frances M. Marr. "Cruelty to Children and its Complications."

Fri. Mar. 3—Dissertation: John M. Garland, Esq. "A Plague on both your Houses."

Wed. Mar. 8—Annual Extraordinary General Meeting.

Fri. Mar. 10—President's Valedictory Address.

# BOOK REVIEWS

*THE PRINCIPLES AND PRACTICE OF MEDICINE.* Edited by Sir Stanley Davidson. 1342 pages. 8th Edition. E. & S. Livingstone. 40/-.

The eighth edition of Davidson is certainly a new edition rather than a reprint. Adhering to the policy of frequent revision to keep abreast of recent developments, all sections have been brought up to date, that on Diabetes Mellitus having been most usefully clarified. In addition two new chapters have been included, one on Genetics in relation to medicine and the other on Acute poisoning.

The study of gentics is becoming increasingly important and a working knowledge of this subject is obtainable from this brief, simplified account.

Acute poisoning is an acute problem as is evident from the alarming rise in the incidence of self poisoning. There are now over 6000 deaths per annum from poisoning in Britain. These facts justify the inclusion of a chapter on this rather specialised subject.

It was once said that Scotland's two greatest exports both cost the same — whisky and Davidson. Despite the increase of 2/6 on Davidson it is now much cheaper than a bottle of whisky. Whether or not it is better value for money depends on your taste.

D.J.M.

*A MANUAL OF HUMAN ANATOMY* (5 volumes sold singly). Aitken, Causey, Joseph and Young. E. & S. Livingstone. 1966.

This series was aimed to give students at the London Schools a concise guide to second M.B. anatomy. The book is precisely written and includes excellent original illustrations. If one is capable of memorizing a book from cover to cover and has no interest in peripheral facts this book is ideal. Most people could, with profit, use the series to highlight the main facts for examination revision.

C.F.J.G.

*DIABETES MELLITUS.* Ed. L. J. P. Duncan. Pfizer Medical Monographs Vol. 1. Univ. Edin. Press. 1966. 42/-.

A subject such as Diabetes Mellitus is one which involves all branches of medicine, and is therefore of interest to all medical practitioners.

This monograph, the proceedings of the first University of Edinburgh Pfizer foundation for Post-Graduate Medical research, presents a very comprehensive and authoritative account of the subject. Its authors include a large number of the Edinburgh teaching staff, as well as experts from overseas.

The work includes sections on the actions and antagonists of Insulin; a description of the complications, and their treatment, and an interesting section on epidemiology. The illustrations are particularly good, and the presentation of the book is a credit to the University Press.

This book deserves a first place in the present works on diabetes mellitus, and should be of great interest to the student and doctor alike.

D.B.

*BASIC DERMATOLOGY.* By P. J. Hare. 198 pages; 61 illustrations. £2.2.0. London; H. K. Lewis & Co. Ltd. 1966.

This little book is a completely new addition to existing works in Dermatology. It is written primarily for the use of medical undergraduates in British medical schools and gives a novel and concise approach to its subject.

The book is divided into three sections. Part I dealing with the general scope of Dermatology, the sort of diseases encountered, and an introduction to the terminology peculiar to this speciality is given. Part II introduces the student to dermatological history taking and discusses the various groups of skin disorders, with emphasis on physical signs and appearances essential in each case to make the differential diagnosis. Part III is an alphabetical list of skin diseases with succinct and up to date notes on their treatment and management.

The book is extremely well illustrated, but all the plates are in black and white which in many cases makes them less informative, though this fault is offset by the relatively low price for a standard text in a medical speciality. I would recommend this book to all students as a foundation for their studies in dermatology, for it will make their lecture courses and clinical instruction far more rewarding.

R.J.N.

*THE ADDICT IN THE STREET.* Jeremy Larner and Paul Tefferteller. Penguin Original. 4/6 net.

"As a habit takes hold, other interests lose importance to the user. Life telescopes down to junk, one fix and looking forward to the next, "stashes" and "scripts", "spikes" and "droppers"." So writes Bill Burroughs, prima donna of the drug-literary scene in his book, "Junkie".

This small compilation deals with the private hells of a few addicts (or more correctly, drug dependents) in the U.S.A. Their poignant stories are faithfully chronicled (by interview); the message comes across starkly. Principally the reader will be struck by the insidious way the habit enmeshes those who find their own problems too much to bear, and then murders the productivity of each individual.

Faced with the conditions some of these people have met in themselves and in others, one cannot help feeling that most people would turn to the high. It is a sobering thought. M.F.M.

*ONE IN TWENTY*, a study of homosexuality in men and women, by Brian Magee. Secker and Warburg. 21/- net.

Homosexuals, Magee asserts, are made, not born. Somewhere along the line in childhood relationships, especially with the parents, a distortion sets in. Traditionally the mother was held as the most important conditioning factor in early development; now it appears that a "recessive" father, not a possessive mother, may be the commonest cause of homosexuality.

Magee has chosen his title with panache. Based on a number of surveys that disclose 4-6 per cent of sample populations to be "predominantly homosexual", the phrase one in twenty is misleading. If Kinsey's proposal of a continuum is accepted, running from the exclusively heterosexual to the bisexual and ultimately to the totally homosexual, then it is a little difficult to see how any firm figure can be set on what is meant by homosexuality. Cultural attitudes have to be indicated, bisexuality, for instance, being rare in the West but common in Muslim countries where it is not forbidden.

But this is a quibble. The general approach is sensible, simple, and very non-camp. The book should clear up one or two misconceptions, and includes a rather coy description of certain sexual procedures indulged in by the homosexual. The depth of this book is not great. In ten years' time it will be very passé. M.F.M.

*AN INTRODUCTION TO MEDICAL AUTOMATION.* L. C. Payne. 125 pages. Pitman. 25/6.

Automation is playing an increasing role in clinical and research medicine but misconceptions and fears about it still abound in the Profession. Dr. Payne's book will do much to dispel these. In a clear and interesting manner, a powerful case for the place of computers in Medicine is presented by a man who is both an enthusiast and a visionary.

He explains the workings and advantages of Electronic medical records systems, computerised laboratory analysis and patient monitoring systems. On the controversial subject of computer assisted diagnosis, far from hammering nails into the diagnostitian's coffin, the book gives insight into how the clinician can use the machine to best advantage. These are illustrated throughout with examples drawn from the author's experience at University College Hospital. The latter half of the book, with admirable clarity and a minimum of maths explains how computers are programmed and how they work.

All those concerned with hospital, group practice or research medicine would do well to read this book.

I.C.M.

*THE CHROMOSOME DISORDERS: An Introduction for Clinicians,* by G. M. Valentine. 126 pages. William Heinemann Medical Books Limited. Price 25/-.

This little book makes an excellent introduction to the study of chromosomes for clinicians and students alike. It is very easy to read and at times even produces a touch of humour. The section on biochemistry of the chromosome is a little too simplified for any budding biochemist but has the advantage of being easily understandable for the average medical student. The early chapters with numerous diagrams and illustrations give a clear account of how chromosome disorders can occur and then go on to describe those that are at present known. Dr. Valentine's account of such disorders as Down's, Turner's and Klinefelter's syndromes, to mention just three, is both intelligible and illuminating. The book has a very interesting chapter on dermatoglyphics and their relation to chromosome disorders which is not documented in any previous work. Dr. Valentine does not answer all the questions but provides enough material to stimulate thought and maybe action. Altogether a very helpful little volume.

T.J.D.

*TEXTBOOK OF OPERATIVE SURGERY.* Eric L. Farquharson. E. & S. Livingstone. 3rd ed. 1966. pp. 950. £6 6/-.

The third edition of this famous text has now made a long-awaited appearance. While there have been important editions and revisions, the book still achieves its aim of presenting the whole field of operative surgery in balanced perspective. Layout and style are similar to previous editions with initial chapters on skin, vessels, tendons, nerves, and the later chapters systematically covering the different regions.

Each section is well-planned and comprehensive. Surgical anatomy and general principles of technique are described; the indications and choice of operation are discussed; the common operations are described in detail and the less common more briefly. Gastro-duodenal surgery is well covered with an interesting discussion on the merits of the operations for duodenal ulcer. There is a definite claim for gastro-jejunostomy as the operation of choice. Operations for hernia are delightfully discussed and described in a most readable manner. The author again quotes his series of over 500 inguinal herniorrhaphies — as out patients under local anaesthesia — a procedure which has not as yet gained general acceptance. Mr. Farquharson's book will continue to be a must for those studying for part II F.R.C.S. and for trainee general surgeons.

D.K.M.

*THE DEVELOPMENT OF THE NORMAL AND ABNORMAL INFANT AND YOUNG CHILD,* by R. S. Illingworth. Third Edition. 378 pages. E. & S. Livingstone Ltd. 1966. 37/6.

This edition contains new chapters on reflextes and reactions of the newborn, the assessment of maturity, assessment for adoption and seeing and hearing. Previous writing has been revised and extended in the light of more recent work. Professor Illingworth's book will undoubtedly continue to be held in the highest esteem because of his thoughtful and clear exposition of the subject. Evidence is succintly presented and areas of ignorance and disagreement indicated. Happily Professor Illingworth avoids becoming embroiled in psychological discussion, writing instead with a firm clinical and practical basis. This delightful book is surely essential for anyone, paediatrician, general practitioner or social worker, who is involved in the developmental assessment of infants and young children.

D.L.W.D.

*REPRODUCTIVE PHYSIOLOGY OF THE POST-PARTUM PERIOD.* A. Sharman. Livingstone 1966. 25/-.

The reconstitution of non-pregnant reproductive physiology following delivery is a complex and confused subject deserving more investigation and certainly needing some clarification. Sharman has here brought together histological and clinical findings from a great number of sources and has condensed them into a usefully correlated review, adding his own findings from investigations designed to close the many gaps in present understanding. The book is broadly in two sections, the one dealing with the reconstitution of the uterus and containing a wealth of histological illustrations, and the other concerned with the reappearance of ovulation and menstruation.

In parts the author has been successful in drawing reasonably definite conclusions, for instance as to the time of the re-establishment of ovulation, but most of the book remains rather confused. Sharman's literary style and presentation does not, perhaps, do justice to his material or to his own investigation; indeed the work is rather dull. But his investigations themselves may be generally criticised for their lack of adequate material for the drawing of conclusions; in particular the final chapter should not have been included for it represents a very poor attempt at scientific investigation.

This is not a book for the undergraduate, but can be recommended to the critical and patient postgraduate for the sheer amount of information presented.

R.H.S.

*BONE MARROW REACTIONS.* J. Yoffrey. Ed. Arnold. 1966. 30/-.

There are still many unsolved facets to the pathophysiological relationship of the bone marrow-blood axis. Professor Yoffrey's contribution to this aspect of haemopoeitic physiology has world wide recognition.

The monograph deals primarily with the quantitative and qualitative response of the various bone marrow cellular components to stress, in a standard experimental animal. Each series is subjected to appropriate stimuli and its reaction outlined from examination of bone marrow and blood.

The book also contains logical conclusions as to the maturation time and life span of the myeloid series.

The chapter on the lymphocytic series is a thorough discussion of this complex series. The nature of the blood small lymphocyte and its relation to the bone marrow one is well reviewed.

In addition to the vast experimental work, the book is a good review of our past and present knowledge of the subject. It will prove to be of great use to research workers engaged in this aspect of haemopoeitic physiology.

A.M.D.

*HORMONE ASSAYS AND THEIR CLINICAL APPLICATION,* by J. A. Loraine and E. Trevor Bell. 584 pages. Published by E. & S. Livingstone, Ltd. 1966. 65/-.

The average doctor, or medical student, has no time for the tiresome task of pursuing references however significant they appear to be; he needs a short, clear and concise text which must also be authoritative. These demands are fulfilled by so few modern textbooks that it is a pleasure to review one that achieves this objective. The authors present a thorough survey of the present trends in endocrinology from the point of view of hormone assay. The chapters on oestrogens, growth hormone and the gonadotrophins are especially to be recommended. This novel approach to the subject of endocrinology should especially recommend itself to the chemist, biochemist and experimental worker, but to the interested student this book is a mine of relevant information. Apart from full descriptions of hormone assay techniques, the physiological role of hormones and their relation to pathological states are summarised. This book is not easy to read, but, as in every science, in endocrinology there is no royal road to effortless understanding. Nowhere can a little patience and effort be so royally rewarded as in the reading of this text.

The authors and publishers, alike, are to be congratulated on producing a book that is up to date, complete and superbly presented. At the price, few endocrinologists can afford to be without this text, which should also be read by all students as an example of how a textbook should be presented.

J.A.H.

*SPATIOCARDIOGRAPHY, Textbook and Atlas,* by V. Laufberger. Published by H. K. Lewis.

Unipolar electrocardiography records the electrical events of the heart from a number of individual points. Vectorcardiography does so in three planes, one at a time. Spatiocardiography demonstrates them in three dimensions simultaneously. Professor Laufberger has written a detailed mathematical analysis of this

difficult subject and its recording techniques. Unfortunately, the clinical discussions are quite inadequate and their translation is obscure and misleading. The book fails in its object of clarification and its complexity will recommend it chiefly to those players of three-dimensional chess who have a working knowledge of Czech.

D.G.J.

*HUMAN NUTRITION AND DIETETICS.* 3rd Edition. Davidson and Passmore. Livingstone. 1966. 95/-.

In its seven years this text has already run into three editions, the two previous each having demanded reprint. It has in the past been reviewed as "sparkling", lucid and "one of the most important books reviwed". Its scope is leviathan, ranging from an unusually clear account of fat metabolism which will be of great value to the pre-clinical undergraduate, to considerations of the population problem and contraceptive techniques.

The present revision has been undertaken with meticulous care and precision as is evidenced by the extensive list of references, and by the directions, at many points in the text, to various useful texts and original papers. There are many good reviews of recent work in the physiology section, and the clinical sections are no less well informed. Each section, in fact, has been revised, and not a few completely rewritten, while the original layout has wisely been retained.

The most outstanding feature of the text is its readability, a further recommendation to the wide range of potential readers, for while it is probably the most authoritative textbook of Nutrition and Dietetics, and a useful reference work for pre-clinical students, it is also worthy of a place in the shelves of any public library.

R.H.S.

*CASUALTY OFFICERS' HANDBOOK.* H. Ellis. 2nd Edition. Butterworths. 1966. pp. 250. 48/-.

This book is intended as a guide for the newly qualified doctor working in a casualty department. As such it fulfils its purpose admirably. Principles of diagnosis and immediate treatment of major surgery emergencies are dealt with in principle, and treatment of minor casualty cases, so often neglected in the large surgery textbooks, is set out in detail.

Injuries to different parts of the body are covered systematically with further chapters on burns, foreign bodies, the acute abdomen and resuscitation. There is well illustrated guidance on X-rays — both on views required and interpretation — with a useful list of lesions commonly missed.

New chapters deal with multiple injuries and on fractures of the facial bones, and the book concludes with a useful chapter on the legal aspects of casualty work.

True to its title this is obviously a comprehensive text but the clear layout of relevant information and the excellent illustrations make this book a "must" for the new casualty officer and thoroughly recommended for clinical student.

I.C.M.

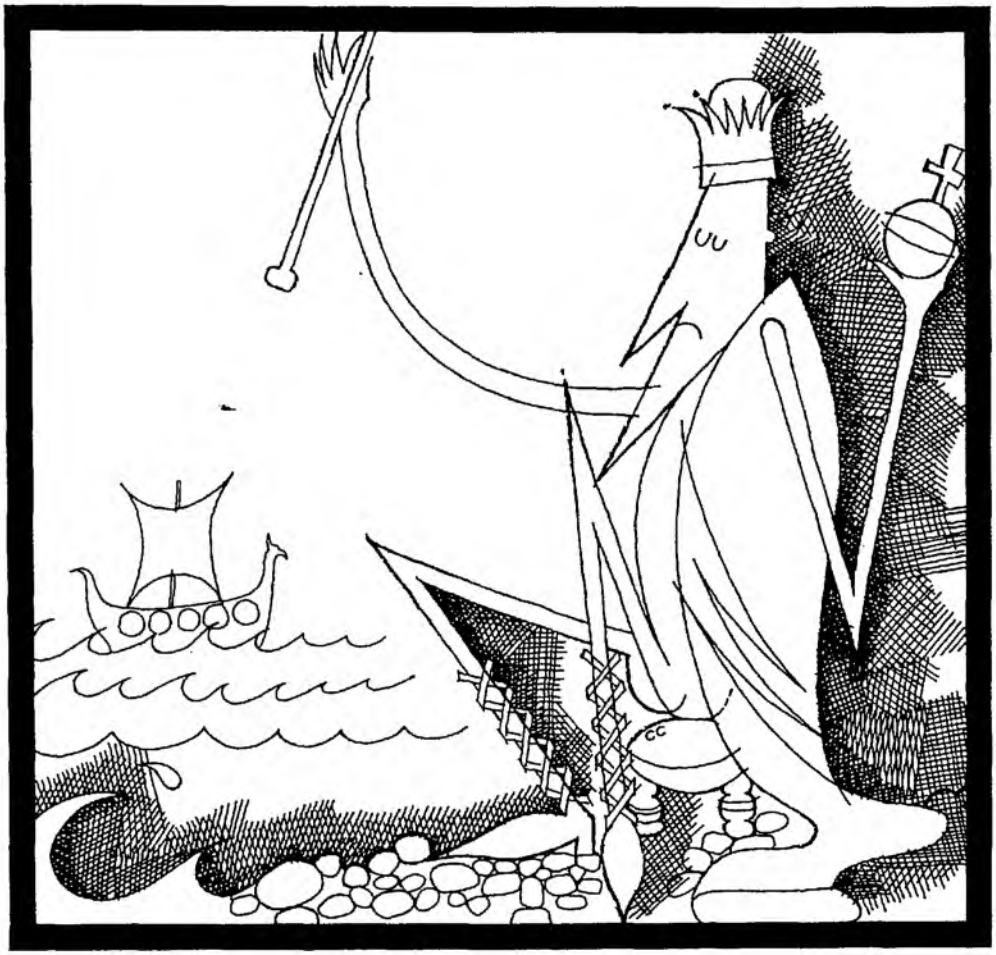
---

## DIAGNOSTIC PROBLEM (from page 25)

*Diagnosis :*

Lead poisoning. Confirmed by the finding of basophilic stipling of the red cells. Subsequent inquiry revealed that this man was exposed to molten lead in his occupation.

Treatment by the chelating agent sodium calcium edetate, 2g daily by intravenous infusion in 5% destrose solution, brought about alleviation of symptoms, decrease in punctate basophilia and increase in urinary lead.



# Canute couldn't stem the tide

## We can tide you over when you are sick

Whoever you are—whatever you do—we have a wide range of personal insurances designed to meet your needs. Our long term **Sickness and Accident Insurances** have bonuses allotted irrespective of claims. We offer **Life Assurances** to provide for your old age and your dependants. There are **Special Policies** for Students and newly qualified Practitioners.

*The Medical and Dental Profession's own Insurance Company*

**MEDICAL SICKNESS ANNUITY AND LIFE ASSURANCE SOCIETY LIMITED**

PO Box 449, 7-10 Chandos Street, Cavendish Square, London W1
Telephone Museum 1686

Printed for McKenzie & Arthur (Publications) Ltd., George Street, Edinburgh, by The Galloway Gazette Press, Newton Stewart, Wigtownshire, Scotland.