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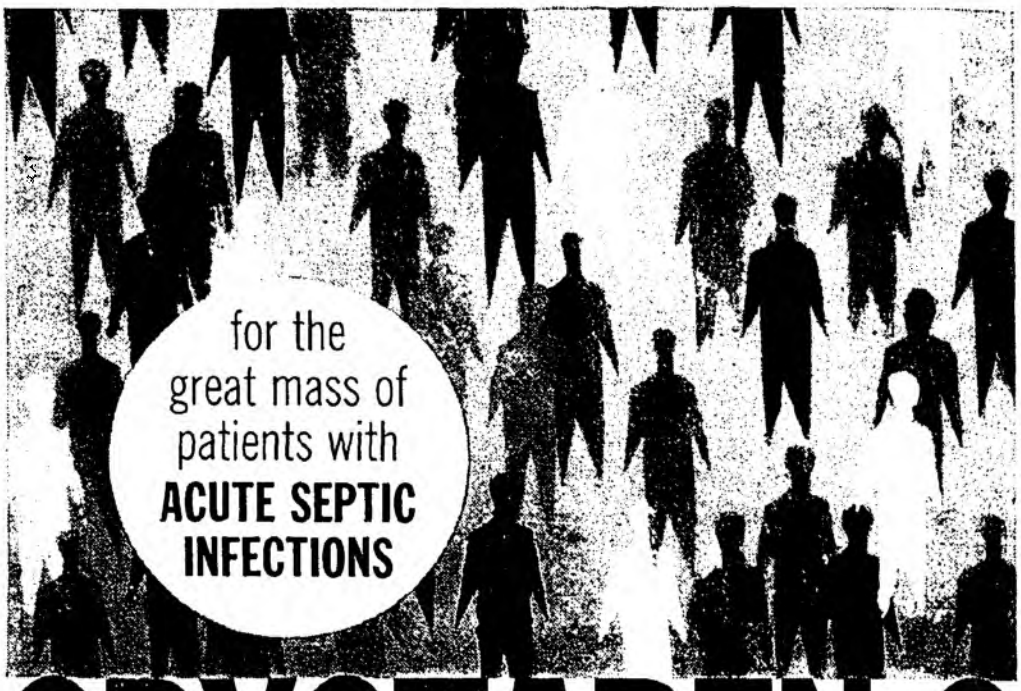

CRYSTAPEN G

INJECTION · TABLETS · SYRUP

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METABOLIC MISTAKES

From a dissertation given by M. Higgins, B.Sc.

For many physicians the inborn errors of metabolism represent a somewhat esoteric group, unlikely to be encountered in clinical practice. Many more diseases have been added to the list of "inborn errors" in the last few years and these diseases can no longer be considered as rarities.

The concept of "inborn errors of metabolism" was introduced by Sir Archibald Garrod in 1908, when he suggested that four metabolic disorders:

albinism
alcaphenuria
cystinuria
pentosuria

had certain features in common.

These features were four in number.

1. The onset of symptoms or signs could be traced to the first few weeks of life.

2. A familial tendency was noted in many cases.

3. These diseases were relatively benign in nature.

4. In many cases the disease showed itself in the progeny of consanguineous marriages.

Before consideration of the clinical aspects of some of these diseases it is valuable to discuss the genetic principles involved in inheritance of disease and its expression within individuals.

Classically genetic defects are transmitted by one of three modes of inheritance.

Namely, as (1) autosomal dominants; (2) autosomal recessives; (3) sex-linked characters.

In dominant inheritance most of the individuals affected are heterozygous for the abnormality. Occasionally however, two affected individuals will mate and produce an offspring who is homozygous for the trait concerned. Such an individual usually has a more severe form of the disease than either of his affected parents.

A recessive gene will only be expressed in individuals who are homozygous for the condition.

As a general rule the following findings suggest a recessive mode of inheritance.

1. The great majority of the affected persons are the offspring of parents who are normal in outward appearance.

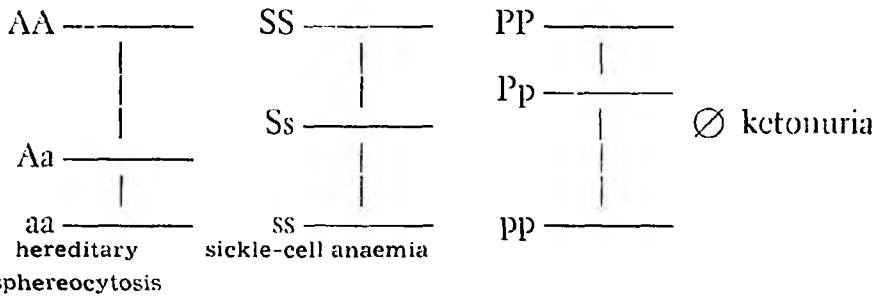
2. The condition tends to affect the siblings in a family, but does not usually affect parents or offspring unless there is intermarriage between close blood relatives.

3. There is an undue proportion of consanguineous marriages among the parents of affected persons. Thus consanguinity occurs in about 80 per cent. of the parents of phenyl-ketonuries, which is considerably higher than the one per cent. seen in the population as a whole.

The classical example of a condition transmitted by sex-linked inheritance is that of haemophilia. Since haemophilia is a recessive trait the offspring, if female will show no clinical disease, but can transmit the abnormality to her male offspring who will display all the stigmata of the disease.

FACTORS AFFECTING EXPRESSION OF GENES

I. It should be emphasised that genetic conditions are seldom completely "dominant" or completely "recessive". This is best illustrated by the following examples :—



In hereditary spherocytosis the heterozygote has anaemia, spherocytosis, increased red cell fragility and all the characteristics of the clinical disease. The homozygote with the two abnormal genes (aa) occurs rarely, but upon investigation of such an individual, his condition is little different from that of the heterozygote — except that the haemolytic process may be a little more severe. Yet, although clinically similar, the genetic make-up is quite different and the condition is regarded as being transmitted as a "dominant".

In sickle cell anaemia the heterozygote (Ss) has about 40 per cent HbS + 60 per cent HbA in the blood. This places it as intermediate between the affected homozygote (ss) and the normal (SS). Such conditions may be regarded as being neither completely dominant nor completely recessive.

Finally in ∅ ketonuria the heterozygote Pp is almost normal in every way. Such patients may have some difficulty in handling large amounts of ∅ alanine as compared with the normal individual (PP).

Thus genetic conditions only appear to be dominant or recessive, depending upon how well one can distinguish between the heterozygote and the normal and the heterozygote and the homozygote with two abnormal genes.

II. While genes are regularly transmitted they are not always expressed in an individual. Thus in some conditions an abnormal trait may "skip" a generation, and only careful study will show some minor degree of the abnormality in the "skipped" generation.

III. A trait which is truly inherited need not necessarily be present at birth but may appear later in life (despite Garrod's original comments upon the nature of inborn errors). The most tragic example of such a disease is probably that of Huntingdon's chorea in which the individual develops marked mental deterioration with involuntary movements etc. at the age of 30 - 40 years.

EXPRESSION OF THE INBORN ERRORS OF METABOLISM

It is not possible to discuss here the mechanism of protein synthesis and gene reproduction. Let us consider, however, a known example of the primary effect of a gene upon a specific molecule within the body.

This may be illustrated by considering sickle-cell anaemia. As mentioned earlier it is known that in this disease two forms of haemoglobin are present

in the blood of affected individuals — HbA + HbS. Now the exact gene responsible for the presence of HbS cannot be identified as yet.

However, on analysis of the globulin moiety of both HbA + HbS it can be shown that there is a difference of one amino acid only, i.e.

HbA - Hist - Val - Leu - Leu - Thre - Pro - Glu - Glu

HbS - Hist - Val - Leu - Leu - Thre - Pro - Val - Glu

This simple difference has far reaching effects on the I.E.P. and hence the solubility of HbS is much less than the solubility of HbA, with the resultant tendency to haemolysis of red cells containing HbS and the stigmata of sickle-cell anaemia.

So far only protein molecules appear to be involved in the primary gene effects of the hereditary disorders.

CLASSIFICATION OF INBORN ERRORS

It is convenient now to classify inborn errors as to the way in which they express disturbances in protein molecules. Three main types may be distinguished according to Hsia.

1. Disturbances in the structure of the protein molecules whereby there appears to be a change in the actual shape or arrangement of the molecules themselves.

2. Disturbances of synthesis of the protein molecule whereby an enzyme is not properly made, or may be entirely absent.

3. Disturbances in the function of the protein molecule, where an enzyme is either absent or not functioning properly.

It is obvious that any classification is highly tentative and until we have more information regarding the "gene effect" then no definite and accurate classification will be possible. Space allows only of the description of a few of these diseases and we may now consider some of those disturbances due to enzyme defects or malfunction.

These represent for most of us the "classical" inborn errors of metabolism and best known among these are the defects in the metabolic pathways of the aromatic amino-acids.

The normal pathways of phenyl-alanine and tyrosine metabolism are shown in Fig. 1 and the site of enzyme defects by Roman numerals.

I. ∅ ketonuria is a hereditary condition, characterised by mental retardation and the presence of phenyl-pyruvic acid in the urine. Nearly 400 cases have been reported since the first cases were described by Folling in 1934.

Clinically, the children found to be suffering from this disorder are noted for their unusually attractive features in infancy. Unlike many mental defectives they show only a slight reduction in stature and head size. Many of the children have blonde hair, blue eyes and a fair skin. A few show a tendency towards developing eczema.

Neurologically no change in muscle here can be demonstrated, but there is an accenuation of both the deep and superficial tendon reflexes. The majority of patients have an I.Q. of 30 or less.

PATHOGENESIS

As indicated ∅ alanine is normally converted to tyrosine by the enzyme ∅ alanine hydroxylase.

Mitoma et al. have shown that two protein fractions are involved in this reaction; a labile fraction I, which is present only in the liver; and a more stable fraction II, which is present also in the kidney and heart. The system requires DPNH and the overall reaction appears to occur in one step with no intermediates.

Recent studies have shown that in ∅ ketonuria fraction II is present in the tissues in normal amounts and that the disease occurs because of a deficiency of fraction I in this enzyme system.

An excessive accumulation of ∅ alanine in the blood and CSF thus results.

This has three effects.

1. Excess ∅ alanine is converted by a transaminase to ∅ pyruvic acid which is converted to

∅ acetic acid
∅ lactic acid
∅ actetyl glutamine

and excreted in the urine.

2. The excess ∅ alanine also inhibits the normal pathways of tyrosine metabolism. There is a fall in melanin production, and this is responsible for the light pigment in the skin and hair of such patients. There is also a disturbance in adrenaline production, since ∅ ketonuries have unusually low blood adrenaline levels.

3. The amino acid excess may also be responsible in some way for the CNS damage, which is characterised by mental retardation, epileptic seizures and abnormal E.E.G. changes.

Diagnosis can now be established early in life by the simple screening procedure using phenistix (effectively, acidified ferric chloride).

Treatment is based upon a diet free of ∅ alanine consisting of a protein hydrolysate.

Associated with ∅ ketonuria as a disorder of the aromatic aminoacids is tyrosinosis, first described in 1932 by Medes.

In the patient described, there was a continuous excretion of P-OH-∅ pyruvic acid, but no other clinical signs. Recently, Felix and his co-workers have made similar observations on two patients with liver disease. The mode of transmission of tyrosinosis is completely unknown and the disease itself is extremely rare. In 26,000 reducing urines tested not one gave a positive reaction to Millon's test.

Tyrosinosis appears to be due to a congenital absence of the liver enzyme P-OH-∅ pyruvic oxidase, which requires glutathione and either vitamin C or dichloro-phenol-indophenol as cofactors. If the protein intake increases or dietary tryosine is increased the amount of P-OH ∅ pyruvate in the urine will increase. The following substances also appear in the urine.

Tyrosine
∅ lactic acid
3.4 D.O.P.A.

On the other hand if homogentisic acid is fed to the patient P-OH-∅ pyruvate does not appear in the urine i.e. the block is at site II in Fig. (1).

No treatment is required for this condition.

The third condition associated with the aromatic amino-acids is that of Alcaptonuria, which is characterised by the excretion of homogentisic acid in the urine.

Apart from the discolouration of the urine, there are no clinical manifestations until the second or third decade, when ochronosis begins to appear. This consists of ochre-like pigments in various parts of the body.

The deposits are particularly prominent in the sclera on either side of the corneal limbus, in the ears and nasal cartilages, and in the superficial tendons of the hand.

By the time such patients reach middle age they usually complain of pain and stiffness in the large joints, owing to a deforming arthritis. X-ray examination shows the presence of thin, densely calcified intervertebral discs.

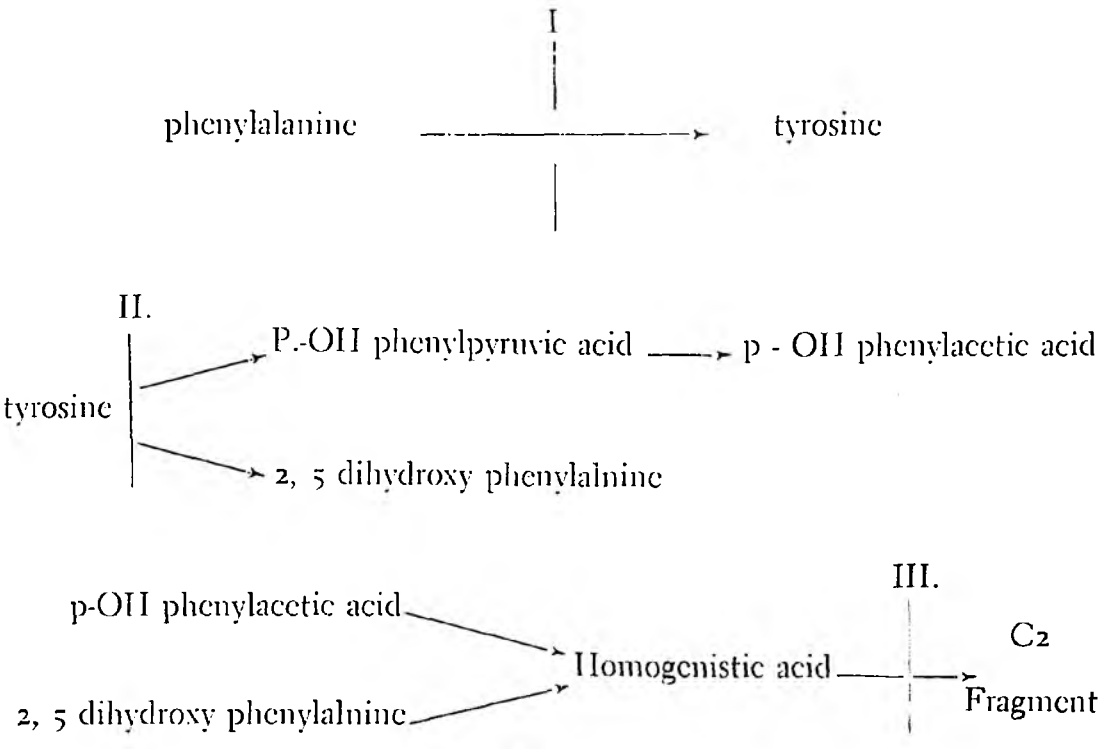


Fig 1.

In most cases alcaptonuria is transmitted as an autosomal recessive trait, but in some instances it appears to be transmitted as a simple dominant. In these families the affected individuals must be regarded as heterozygous for the condition.

It would thus appear that there are two types of alcaptonuria, which are not related to each other. As yet it is not known whether the two types are alleles or at different loci on the same chromosome.

As the feeding of homogentistic acid to alcaptonurics results in almost quantitative recovery of that substance from the urine, it is postulated that the block exists as shown at site III in Fig (1). This has recently been confirmed in a patient with alcaptonuria.

The treatment of this condition is confined to the symptomatic treatment of the arthritis.

Albinism, as the name implies, is characterised by a complete absence of pigment in the skin, eyes and hair. The pupils appear to be red and the iris is pink or bluish from reflected light.

Astigmatism
Photophobia (are present in varying degrees)
Nystagmus

The hair is fine and white or very pale yellow in colour. The condition is transmitted as a simple recessive, as is shown by the fact that 20 - 30 per cent. result from marriages between cousins.

The pathogenesis of albinism appears to be due to the absence of the enzyme tyrosinase from the melanocytes of the skin.

These pigment-producing cells have been shown to be present in normal amounts in such patients, but the enzyme's absence ensures no melanin is produced.

The action of tyrosinase is :

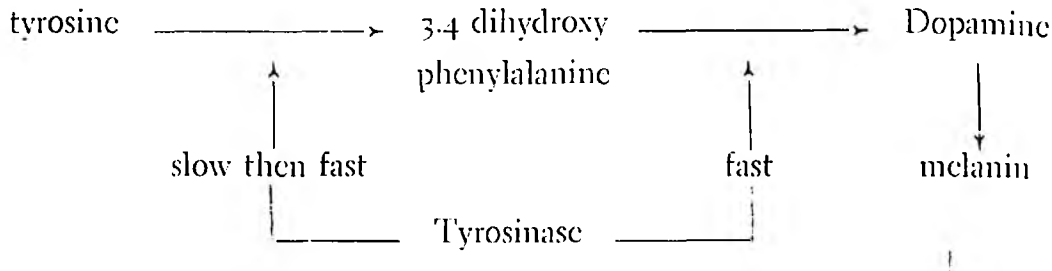


Fig. 2.

Tryosine is not converted to DOPA in the absence of Tyrosinase and absence of the enzyme results in a complete block.

Clinical examination is usually sufficient for diagnosis and treatment consists of prevention of exposure to sunlight and proper protection of the eyes by dark glasses.

The classification of diseases used in this artcile was taken from "Inborn errors of metabolism" by Hsia published by Year Book Medical Publishers Inc.

EDUCATION IN THE MEDICAL SCIENCES

By Professor W. L. M. PERRY, O.B.E., M.D., D.Sc.

I have recently asked the 4th year medical students, in a questionnaire, a number of questions about the course in Pharmacology which they are about to complete. The answers have made fascinating reading and have brought into focus many of the vague feelings about medical education that have been in the back of my mind for some time.

There are a few general conclusions that one can draw from the collective views of medical students surveyed in such a way. Perhaps the most striking is the singular absence of any degree of unanimity. It may be taken as virtually certain that any topic, treated in any one way, taught by any one method and by any one person, will please one third of the class, displease another third, and leave the rest absolutely cold; it will interest one half of the class, the other half finding it dull; one half, composed of quite different students, will consider it useful, the other half useless. This is a slight over-simplification for occasionally there is a concensus of opinion so that sometimes even 80% of the class will agree. By and large, however, one is left with the doubtfully comforting reflection that one can never please more than about half of one's audience; and that, therefore, to select what to teach and the way in which to teach it on the basis of one's own experience and opinion is just as likely to be acceptable as to take a great deal of time and trouble trying to design a course to suit the views of anyone else student or otherwise. Perhaps the teacher does know best after all!

If this is the most striking finding the most surprising one, to me at least, is the clearly expressed view that students do not expect to enjoy the course. They seem to have a great desire to mortify the flesh. Thus 9 out of 10 students think that writing essays is a valuable way of learning, but less than half enjoy writing them. Again, 2 out of 3 students enjoy lectures that provide the experimental evidence for important conclusions but only 1 in 4 considers that lectures should usually aim to provide this. On the other hand there is considerable evidence that students find lectures that provide a summary of the important facts that are needed for examination purposes dull and boring; but that this is what they think that lectures should usually do. This is a view that I find quite extraordinary and that disturbs me very much. Learning should be fun, and boredom can never induce intellectual agility. Something has gone far wrong.

Perhaps there is a clue as to what is wrong in another piece of evidence from the questionnaire. While there is, in general, little correlation between the opinion of students and their previous academic record, there is a very high correlation between this past record and their habits of attendance at lectures. Thus 9 out of 10 students who had never failed a degree examination stated that they attended lectures regularly; while 4 out of 10 students who had already had to repeat at least one year of study stated that they attended

fewer than 50% of the lectures. Does this indicate that it is only by sitting through lectures in a state of total boredom, laboriously copying down the material provided, that students can pass examinations? Is this why, after four years of medical education, intelligent students can seriously opt for boredom? This is a desperately serious matter.

I believe that the vast majority of students entering the medical school are full of enthusiasm for their future career, anxious to learn about medicine and ready to put a large part of their youthful energy and effort into their studies. Why has all this been lost after four years? In these four years the whole of the scientific basis upon which clinical practice is based has been covered by the syllabus. Each of the scentific disciplines has an important part to play. Each can be exciting, fascinating, stimulating. Each has students of the Faculty of Science who find excitement, fascination, stimulation. Apparently medical students are different.

The fundamental fault lies, I believe, in the fact that neither the students nor the teachers have a really clear idea of what they are trying to do. Let us consider the students first.

Medical students are all going to be "doctors". This does not define their academic aim in any way at all. In the minds of most students it is associated not with academic education, but with the glamour of clinical work, the human relationships with patients and the idea of social service. It is consequently related only very vaguely to the rigorous disciplines of the medical sciences. These are regarded as the background, often accepted as necessary only with reluctance, to a clinical training. Modern clinicians are aware of, and often very vocal about, the fact that the medical sciences are no longer the background but are much more often the main feature of the clinical picture, but it seems to be very hard for the student to accept this. In consequence the acquisition of the background is not generally regarded as an activity that demands the whole of his energy and attention, which are held in reserve for his "vocation", the care of patients. I am very far from sneering at this view; it is wholly admirable when considered in a moral or ethical context. I do believe that, however admirable, it is based upon a total misconception of the nature of patient care today. The natural result of all this is that the medical sciences come to be regarded as academic obstacles placed in the path of the aspiring doctor by an unsympathetic faculty which is far too scientifically-minded. This engenders the state of mind with which we are all familiar and which is common to medical schools all over the country; a state of mind which rebels at any demand for intellectual effort in science, and which asks only to be told what information must be memorised to pass an examination and how such information is applicable to a clinical situation.

I think this is a pretty fair description of the attitude of many a medical student. What he is trying to do is simply to pass the professional examinations and "to get on with clinical work". He has little idea of what his teachers are trying to do. Let us look at them for a moment and see if they know themselves.

It may be taken as axiomatic that all teachers are fascinated by their own subject. If they were not, they would have a miserable time spending all their lives immersed in it; and if they are not, they have no business to be teaching it. Fascination by a subject induces a state of mind in which the greatest possible reward is the feeling that some of the fascination has been passed on to others. All teachers want to catch and hold the imagination of their audience, to stimulate in their students a real interest in the subject.

When teaching an advanced group of students who have elected to make a career in the subject the teacher has little difficulty in establishing a rapport. There is a mutual understanding, a unity of purpose, a communion of scholarship. This explains the attraction of teaching Honours classes in the Faculties of Arts and Science. Teachers of medical students want to achieve something of this too.

Teachers of medical science who, like myself, have qualified in medicine and practised medicine, are, no doubt, a strange bunch. I think that the main reason for our leaving the clinical field is that we found it unsatisfying. The lack of real knowledge, the authoritarian basis of much practice, the routine and unquestioning use of accepted treatment were not, to us, adequately compensated by the human relationships and the social service. These valuable rewards do, in fact, compensate most doctors, and it is just as well that they do. For those whom they don't, the search for answers to the questions provides the only satisfaction. Where such people are teachers, they are acutely aware, from their own experience, that there are still many unanswered clinical questions, and many more to which an answer can be provided only by their own scientific discipline. They know that their students are going to feel, to some extent, the lack of satisfaction they themselves felt in the past. So they naturally wish that they could persuade students that an investment of more energy and attention to the medical sciences would be repayed many times over in a fuller and more satisfying clinical experience in later years.

The fact remains that, despite this, such teachers cannot help being aware of the prevailing attitude of medical students to which I have already drawn attention. Thus the teacher cannot easily accept the single aim of stimulating in the student an interest in his subject. He tends to lower his sights, to accept a new and lower aim, namely that of providing as quickly and as painlessly as possible the background that the student needs. As soon as he does this his courses provide, quite intentionally, summaries of basic established factual information; they become routine, stereotyped. The teacher has no real interest in what he is saying and the student is quick to sense this. There is a total loss of stimulation and a spreading boredom with the whole business. The student, when he encounters this, is reinforced in his belief that all he is doing is going through the preliminary movements before starting the dance in the clinical years. The vicious circle is thus established.

When this situation is discerned great efforts are made to explain and justify it. Students, it is said, are of too low a quality to benefit from a more rigorous intellectual approach; we are training general practitioners and why should they be burdened with the recondite in science; medicine is a technical training not a scientific education; students must not be over-burdened in the early years of a long six year course, they must have a chance to sow their wild oats. These are the pleadings of defeated teachers and find an echo in disillusioned students who use them to excuse their own boredom.

It is, of course, nonsense to accept these excuses. The average medical student is carefully selected for his intelligence. His abilities do not deteriorate; they are never tapped. He is capable of far more than he ever produces. He could well accept the intellectual challenges that are so seldom offered. Modern medicine requires a scientific education, not a memory for some basic scientific facts. Students will always find time to sow wild oats.

But even if we accept all this, we still have to break out of the vicious circle that has been established, and this looks like being very difficult. Teachers cannot do it by themselves. This is what disturbs me on examining the questionnaire replies. We tried last year in Pharmacology to offer some food for intellectual thought, something more than a bare recital of essential information. It seems that we did achieve some stimulation of interest, but this was regarded as a luxury by the students, a luxury that they could not afford. Education is rejected in favour of the acquisition of facts.

Are we to accept this student opinion and provide what is wanted, however dull? Or are we to go on despite unpopularity, providing interest at the expense of increasing difficulty, increasing demand for intellectual effort, increasing deviation from matters of obvious practical clinical application? I believe that we must go on. We must continue to challenge the student, to try to shatter the mental torpor that the system has induced in him. Sooner or later he will react and between us we can break the circle that binds us to the present unsatisfactory position. The curriculum may need changing; but it is not the curriculum that finally determines the state of education, it is the attitudes of student and teacher that are paramount.

HENRY VIII

From a Dissertation to the Royal Medical Society by G. Devonald

This short article could have been aptly subtitled Sex, Syphilis and Sores, because this accurately conveys the impression that most people have of Henry VIII. Mention his name, and a lecherous look comes into a person's eye and he immediately makes some remark about Henry's six wives and his syphilis. So much good and so much evil has been written about him that he must be the most controversial king in British history. Dickens described him as "a blot of blood and grease", yet others have thought him to be the paragon of all the virtues. Religious convictions obviously played their part in colouring the opinions of earlier writers, Henry being Bluff King Hal, the merry, innocent monarch to the Protestant, and a cruel, sadistic ogre to the Catholic. The truth is that both sides were partly right. When Henry came to the throne he was considered to be the most intelligent, most tolerant and most athletic of all European kings. He was kind, considerate and reasonable, even Erasmus thought that his crowning heralded a Golden Age in the English Renaissance. Yet during his early forties a change came over him and he became an irritable, selfish, suspicious tyrant. At that time Castillan, the French ambassador described him as "the most dangerous and cruel man in the world".

But despite all this one thing is certain, Henry VIII was a great king. When he succeeded to the throne England was a second class power in a Europe dominated by France, Spain and the Holy Roman Empire. By the time he died he had by a mixture of skilful and crude statecraft, successful and near calamitous wars and the sudden Reformation of the Church into the Church of England, raised England as a power in international politics.

This then is the man whose health is the subject of this article. Did he have syphilis? To provide the answer to this very controversial subject his personal and family history must be studied closely.

HENRY'S PERSONAL MEDICAL HISTORY

There is little direct evidence of Henry's health, but the reports of foreign ambassadors and the correspondence of men of influence, such as Wolsey provide a very full picture of the king's illnesses.

His first recorded illness ocurred in 1514, when he was twenty-two. Badoer, the Venetian ambassador, described it as measles, but another thought it was smallpox. The difficulty in differentiation sometimes occurs today and it is therefore understandable that mistakes in diagnosis were commoner in the fifteenth century, especially since measles was far more virulent. However, Henry soon recovered and showed no after effects. Then in 1521, when twenty-nine, he had an attack of malaria "which grew to two tertians" and there was "a long continuance of cold and heat". But apart from these episodes the reports in his twenties and early thirties refer only to his good health and his great strength and endurance. His life, at first glance, appears to have been just one long round of hunting and jousting. Indeed one of Wolsey's correspondents points out that during a hunt the king "spares no pains to convert the sport into a martyrdom". He did, however, as a result of his pastimes, have several accidents. For instance in 1521 when jousting with the Duke of Suffolk he narrowly missed being killed when he was hit on the helmet with his visor up. But apart from a severe shaking he suffered no ill effects and was able to run another six courses.

Around about 1526 Henry became infatuated with Anne Boleyn, and in 1527 began divorce proceedings against Catherine of Aragon. In 1528 he began to complain of headaches and the same complaint revived in July and August of that year. Some authors have tried to relate these to the jousting accident of 1521. This seems rather ambitious and it seems just as likely that the headaches were a physical manifestation of his marital and political conflicts. At this time Henry was still a patient man, for he worked for six long years to engineer a divorce from Catherine of Aragon. It was only after his marriage to Anne Boleyn that the change in his character became noticeable. He married her in 1533 and by 1536, when he married Jane Seymour, he was a different man.

The first reference to Henry's legs occured in 1537 at the trial of Lord Montague. He said, "I dreamed that the King was dead, but he will die suddenly, his leg will kill him and then we shall have jolly stirring." In April it was reported that "The King goes seldom abroad because his leg is something sore"; and in June Henry himself wrote, "But to be frank with you, which you must keep to yourself a humour has fallen into our legs." A month later, in May, the king "stopped one of the fistulas of his legs, and for ten or twelve days the humours which had no outlet were likely to have stifled him, so that he was sometimes without speaking, black in the face and in great danger." The physicians were so frightened that when a fistula closed again in 1541 they lost no time in opening it.

The king's obesity became noticeable in 1542, when he was "already very stout and growing heavier". This is understandable because since 1535 he had taken no exercise. He had given up jousting after being unhorsed for the first and last time, and as hunting was a comparatively quiet sport began to get fatter and fatter.

The reports of his "sorre leg" appear frequently, and in April 1542 Chapuys, the ambassador of Charles V, urged his master to persuade Henry not to personally lead his army against the French. He reported that the "King's chronic disease and obesity require particular care lest his life be endangered . . . for however stout-hearted he may be with his age, his obesity and weight, he has the worse legs in the world". Henry ignored all advice and 1544-45 was a period of great physical and mental activity for him. But by 1546 he was weakening and the reports record a story of gradually increasing ill-health. The stories that his obesity and disease made it impossible for him to pass

through doors, and impossible for him to climb up stairs without the aid of machinery, are wrong; but occasionally when his legs were troubling him he did travel in a primitive sedan chair.

The nature of his terminal illness is not recorded clearly. He had several attacks "of burning fever" and on January 27th, 1547, was very ill. He went into a stuporose state and died on January 28th, 1547, at 2.00 a.m.

THE OBSTETRIC HISTORY OF HENRY'S WIVES

Catherine of Aragon. The number of her pregnancies is disputed and range from six to nine. Chamberlin in his book gives the most convincing account and states that there were only six definite pregnancies.

January 31st, 1510. Stillborn girl.
January 1st, 1511. Live boy. Lived for fifty-two days.
September 17th, 1513. Stillbirth or very early neonatal death of a boy.
November 1514. Stillbirth of a boy.
November 1516. Mary.
November 10th, 1518. Still born girl.

So in six established pregnancies the outcome was only successful in two. The second pregnancy resulted in a boy who only lived fifty-two days, and the fifth in Mary.

Elizabeth Blount. She was Henry's first mistress and she bore him a son, Henry, Duke of Richmond.

Anne Boleyn. Married 1533.

She had four pregnancies of which only one, the first, was successful.

1533 Elizabeth
1534 Abortion.
1535 Abortion.
1536 Abortion of a male foetus.

Poor Anne, she really did no better than Catherine. The abortion in January 1536, seems to have been the last straw, and on 19th May, 1536, after a farcial trial, she was beheaded. If she did nothing else during her pregnancies, Anne collected some unusual compliments. Tallyour described her as having "a goodly belly", and Kyngston thought that she had "as fair a belly as ever he had seen".

Jane Seymour. Married 1536.

Jane Seymour appears to have been the only wife that Henry really loved. Therefore it is even more unfortunate that she died so soon after their marriage. She died twelve days after the birth of Edward. The labour was long and difficult so "that she was feign to be ripped". This has been interpreted to mean that she was delivered by Caesarian section, but I think that the description could just as well described a perineal tear or episiotomy.

Anne of Cleves, Catherine Howard and Catherine Parr bore no children. Catherine Howard was the victim of the conflict between Protestants and Romanists and was beheaded. It was suggested, just as in the case of Anne Boleyn, that she, despairing of Henry's ability to sire a child, sought the help of a younger more attractive man. She failed to give Henry what he wanted most, a child, and she died.

RELEVANT MEDICAL HISTORY OF HENRY'S CHILDREN

Mary. She was never a strong girl and the strain of her life with the divorced Catherine of Aragon must have had severe repercussions on her outlook and on her health. She seems to have had a series of illnesses from ammenorrhoea to hysteria, and had the classical pseudocyesis when married to Philip of Spain. However, she did exhibit one sign which is relevant to

whether or not Henry VIII was syphilitic, namely that she had very poor eye-sight.

Elizabeth. There are very few references to her health, but she died of what has been called by some a tuberculous laryngitis. She had difficulty in swallowing and speaking and complained of a swelling of the throat.

Edward. Edward was always very weak and died when only fifteen. He was troubled throughout his life by cough and sputum and died in 1533 after a particularly fierce attack of these symptoms. His terminal illness was described as follows: "The matter he ejects from his mouth is sometimes coloured a greenish yellow and black, sometimes pink like the colour of blood. He is vexed by a harsh continuous cough, his body is dry and burning, his belly is swollen, he has a slow fever upon him that never leaves him." Everyone seems to agree that this describes tuberculosis.

Henry, Duke of Richmond. Henry's bastard son was also weak and consumptive and died when aged eighteen.

This then is the medical history of Henry VIII, the obstetric history of his wives, and the medical history of his children. Upon what facts do the people who accuse Henry of being a syphilitic base their evidence?

(1) Henry had ample opportunity of contracting the disease.

Compared with most kings of that period Henry's opportunities were limited. He was a comparatively faithful husband and throughout his life only had three mistresses, Elizabeth Blount, Mary Boleyn and Anne Boleyn. Elizabeth Blount has never been accused of transmitting syphilis to Henry. Her obstetric history appears to have been free from any syphilitic stigmata, for she had one pregnancy which terminated successfully in the birth of a normal child. Mary and Anne Boleyn are not, however, above suspicion. They lived for some time at the French court "which even in those days of licentiousness enjoyed an undesirable pre-eminence in profligacy." In fact, Mary Boleyn, because of her shameful behaviour became known as the English Mare.

There has been some suggestions that portraits of Anne show an ulcer beneath her chin. Professor Shrewsbury thinks that this may account for Henry's dreadful treatment of her. He was not satisfied with divorcing her, but had also to bastardise her daughter, tear her character apart in her farcial trial then execute her. Disease had always frightened him and if he had been in contact with the dreaded disease, it would have made him, to say the least, angry.

Catherine of Aragon may have infected Henry. Admittedly, she claimed that her first marriage to Henry's brother had never been consumated, but Arthur was heard to boast that he had been "six miles into Spain". He may have infected Catherine and she in her turn Henry.

However there seems to be little point in listing all the possible sources of infection. There is no doubt that even if his consorts were not syphilitic, he may have contacted the disease by non-venereal means, which was a commoner mode of spread than nowadays. Therefore it must be agreed that Henry had ample opportunity of catching the disease.

(2) Henry exhibited signs and symptoms of syphilis.

There is no reference in any of the Tudor documents that Henry had syphilis. The disease at that time was even more virulent that it is today and the Tudor physicians recognised it and treated it. Foreign ambassadors, who lived at the court, who missed nothing, who were willing to bribe anyone for any information were hardly likely not to mention an illness which took six weeks of mercurial treatment to cure. Catholics anxious to discredit him were hardly likely to miss such an ideal opportunity. Yet despite this Henry was accused of having syphilitic leg ulcers and involvement of the central nervous system.

Henry's leg ulcers were associated with swollen legs, they were chronic, frequently extremely painful, and were present on both legs. Syphilitic ulcers do not conform to this pattern of symptoms. They may appear on both legs, especially at sites of trauma and around the joints, but are always painless. Ulcers due to subcutaneous gummata heal themselves with or without treatment, and those due to the breakdown of an underlying osteitis would be associated with pathological fractures. Chronic syphilitic ulceration is not unknown, but again is painless.

Probably the most attractive theory as to the causation of the ulcers is that which suggests that they were due to varicose veins and stasis. This would account for the painful nature of the ulcers and also for the swollen legs. Rest is essential for the treatment of these varicose ulcers, but Henry was a difficult, active patient. Therefore they became chronic. An extension of the inflammatory process to involve the deep veins with thrombosis, with the subsequent throwing off of a thrombus, pulmonary embolus and infarction would lead to the symptoms of 1538, when he became black in the face, dyspnoeic and distressed.

Professor Shrewsbury has put forward the theory that Henry inherited gout from his father. The breakdown of tophi near the ankle, knee and hip would account for the multipilicity of lesions; the crystals working their way up through old or new fistulae for the severe pain; and the nature of the disease for the intermittency of symptoms. This is an extremely interesting theory, but Henry, although given to surfeits, never complained of joint disease.

Some people have suggested that Henry's change in character was due to syphilis of the central nervous system. Admittedly in the latter part of his life he became cruel and easily roused to anger and was subject to headaches, but he showed no other signs or symptoms. He was never forgetful, never unable to concentrate, never subject to mental aberration, and never lost control of his country's affairs.

From the available evidence it seems unfair to brand Henry as a syphilitic just because he had ulcers and just because he had a change in character.

(3) The obstetric history of his wives, especially of Catherine of Aragon, suggests that they were infected with syphilis by Henry.

Catherine of Aragon's pregnancies form the trump card of those who say that she was infected by Henry. Until Chamberlin wrote his book, the accusers stated that she had had nine pregnancies of which two only ended successfully. They then pointed out the number of stillbirths and quoted the textbooks and experts as saying that syphilis causes premature labour and stillbirth. Nowadays the figure of six is accepted as correct for the number of pregnancies and the textbooks have been read a little more carefully. Syphilitic infection of the mother does result in premature labour and stillbirth, but the sequence of pregnancies is characteristic. In an untreated syphilitic woman the first pregnancy ends in early labour and stillbirth and subsequent pregnancies terminate in the same way, but each one later until, at last, a living, but syphilitic child, is born. This sequence of events did not occur in Catherine's case, the first live child occuring too early, and the last stillbirth too late. There is also no evidence that either the living boy or Mary showed any evidence of congenital syphilis. Therefore, there is no evidence that Catherine's pregnancies were affected by syphilis.

Anne Boleyn's pregnancies also do not fit in to the syphilitic pattern. She had three abortions, but syphilis does not characteristically cause termination of pregnancy before the twenty-eighth week. Therefore, there is little evidence that her pregnacies were affected by syphilis.

The accusations that Henry infected Anne Boleyn and Catherine of Aragon

with syphilis, and that this affected their pregnancies appears to be based on very poor evidence.

(4) Henry's children showed signs of congenital syphilis.

Elizabeth, Edward and Henry, Duke of Richmond had no signs of congenital syphilis. Their portraits show none of the stigmata of the congenital disease and their medical history has no reference to it.

Mary had one complaint which is emphasised by Henry's accusers. She had very bad eye-sight. This is characteristic of syphilis when it forms part of Hutchinson's Triad, i.e. interstitial keratitis leading to blindness, Labyrynthitis leading to deafness and the characteristic deformity of the teeth of the second dentition. Mary showed neither of the latter two signs and it is therefore unfair to label her as a congenital syphilitic just because she had bad eye-sight. Her portraits do not support any idea of congenital syphilis.

CONCLUSION

Henry VIII had ample opportunity to contract syphilis, but the evidence for him having done so is flimsy. There is no reference to him having any of the signs and symptoms, his wives appear to have been unaffected and his children were not congenital syphilitics. Therefore, it must be concluded that he did not have syphilis.

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RES MEDICA

THE ROYAL MEDICAL SOCIETY

226th Session

THE SOCIETY

The business of the Society has once again been successfully completed. Our thanks are due to the outside speakers who so readily agreed to give addresses and talks, particularly to those who travelled considerable distances to do so. Members themselves, however, continued to contribute most of the Society's public and private business. The dissertations maintained their usual high standard, three of them are published in this issue of *Res Medica*. A full programme of outside visits and social functions has been held, the Guest of Honour at the annual dinner being Professor Emeritus Norman M. Dott.

The agenda for next session is currently in preparation, and already includes the names of several prominent outside speakers. With Mr Robin Ewart as Senior President, the session promises to be a most successful one.

THE APPEAL

The future of the Society has been affected by several important developments during the year.

The Society was informed early in the session that the Midlothian County Council has speeded up its plans, and now intends to acquire the present Hall by compulsory purchase within two years' time. Their previous scheme had envisaged our removal in about ten years.

With the co-operation of the University, plans are in hand for the Royal Medical Society to build a completely autonomous New Hall on the site of the proposed Student Amenities Centre. It is welcome news that work will start on clearing this site earlier than had been anticipated—probably in 1965. The estimated cost of such a building is not as high as had been feared, and it also seems likely the value of the present hall will prove to be higher than at first thought.

Thus although the need for new premises has become more urgent during the session, the prospect of obtaining a new hall has become brighter, provided the necessary financial support is received.

NEW LAWS

Next session the triennial meeting to review the laws of the Society falls due. As a preparatory measure, a committee was appointed in February to suggest ways of improving the laws, particularly with a view to attracting more members. In a preliminary report, the committee suggested that business meetings similar to the present 1st. private business should be held on only three evenings each term, so that the first hour of the other meetings could be used for the discussion of topics of interest to preclinical as well as clinical medical students.

Such a change would necessitate considerable streamlining of the Society's procedure, to enable business matters to be completed in the much shorter time available. With this in view, the committee produced a revised version of the laws incorporating the proposed changes, together with a number of time-saving alterations to the procedure for the election of members, fellows, etc. Provision is also made for the election of a Private Business Committee to arrange business for the early part of each meeting, and to share some of the duties of the over-worked Public Business Committee.

At the final 2nd Private Business of the session it was unanimously decided that the revised laws should be brought into effect with the force of regulations for an experimental period from the start of next session until February 1964, when the whole position will be reviewed at the statutory triennial meeting.

THE PHARMACOLOGY OF SOME HYPOTENSIVE DRUGS

The arterial blood pressure is controlled by the autonomic nervous system. Information about the level of arterial pressure is obtained from the receptors in the aortic arch and carotid sinus together with those situated in the heart. Generalised arteriolar constriction increases the total peripheral resistance and hence the blood pressure; conversely arteriolar dilation results in a fall in blood pressure. Normally peripheral arteriolar constriction is brought about by release of noradrenaline and adrenaline from sympathetic nerve endings, or by the release of adrenaline from the adrenal medulla. The same mechanism is responsible for increase in vasomotor tone and, in part, for the mechanism responsible for increase in heart rate. The anatomical pathways for these reflexes are :

(a) Carotid sinus.
(b) Hypothalmus, midbrain and spinal chord.
(c) Sympathetic ganglia.
(d) Sympathetic post ganglionic nerve.
(e) Peripheral adrenergic receptors.

Many drugs acting on the central nervous system cause a fall in blood pressure; even sleep induces such a change. Rises in blood pressure in stress and emotion are reduced or abolished by tranquilisers, e.g. chlorpromazine or sedatives such as barbiturates. Meprobamate is thought to cause block of spinal interneurones and also has a hypotensive effect. A more active analogue, membutamate was discovered. This drug causes a fall in blood pressure in the renal hypertensive rabbit. In man it has a hypotensive effect lasting six hours. It does not alter the cardiac output or cause any obvious haemodynamic changes. In crossed circulation experiments in the dog, where one limb was

isolated except for a connection by the sciatic nerve, a significant increase in the blood flow in the isolated limb following a membutate injection was observed. This suggests that the prime site of action is in the central nervous system, but its place in therapy, if any, has not yet been determined.

Another drug of particular interest belonging to the tranquilliser group is reserpine. Adrenaline, noradrenaline and often 5 hydroxy-tryptamine occur in granules in the brain, sympathetic nerve endings and chromaffin tissues. These are probably associated with A.T.P. The A.T.P. occurring at these sites has been shown by radio-tracer experiments to be far less labile than that occurring in other tissues. The ratio of A.T.P. to catecholamine approximates to 1 : 4.

Brodie, in 1956, showed that reserpine depleted the brain of serotonin and suggested the probability of it having its main effect via central mechanisms. Later Maxwell showed that the drug also depletes the brain of catechol amines. Carbeau and his co-workers then showed that reserpine causes adrenaline and noradrenaline depletion in the nerve endings, and also that it has a direct relaxing effect on smooth muscle. Reserpine, unlike chlorpromazine, does not decrease sympathetic activity passing into the ganglion. Thus it is no longer certain that the hypotensive action of reserpine is central.

An analogue of reserpine, syrosingopine, in which the trimethoxy phenyl group is replaced by a dimethoxy-propyl phenyl group, has been synthesised. It was found that 25 mgms of syrosingopine depletes the peripheral nerve endings at catechol amines whilst 800 mgms. are needed before depletion of central catechol amines takes place. At the lower dose level syrosingopine has a hypotensive but not sedative effect. Tetrabenasine depletes central catechol amines but not peripheral amines and does not have a hypotensive action. It is, therefore, probable that the sedative action of reserpine can be regarded as distinct from the hypotensive and to be the result of central action. The peripheral action of reserpine is depletion of catecheol amines at the nerve endings with consequent hypotension. It has been shown that if catechol amine content of the nerve ending falls below 10% of the normal level transmission to the effector organ ceases. Dopa has been shown to be taken up rapidly by the reserpinised animals and converted to noradrenaline. However, on analysis, the noradrenaline was found only in the intracellular sap suggesting that the depletion is a result of interference in the storage mechanisms.

Just lately some new hypotensive drugs acting on the post-ganglionic nerve have been discovered. Bretylium tosylate was originally introduced by Bourra. This drug when given intravenously in the cat first causes pilocrection, rise in blood pressure and other sympathomimetic effects. Later it causes hypo tension. Bretylium does not cause depletion at the nerve ending but neither does it block transmission at the ganglia. It does not, in any way, antagonise the effect of reserpine. Bretylium, in high concentrations has been shown to act as a local anaesthetic. It is now thought that it acts by blocking transmission at the nerve terminals resulting in a failure to release noradrenaline.

Another drug recently introduced and acting on the postsynaptic nerve is guanethidine. Chemically the drug is unusual, it contains an eight membered ring and a guanide group. The drug causes depletion of catechol amines in the nerve endings but not in the adrenal medulla or the brain. It also has some ganglion blocking activity. Like bretylium; guanethidine has some sympathomimetic activity but whether this is due to release of noradrenaline or a direct action of the drug is unknown. This drug in no way inhibits the action of injected noradrenaline or angiotonin implying that the point of

action is before the effector site. Transmission has been shown to be depressed at the ganglion but not sufficiently to account for the hypotensive effect. Similarily post ganglionic stimulation did not cause contraction of the smooth muscle effector organ. In certain preparations guanethidine has been shown to enhance the action of acetyl choline. Now on Burn's theory of adrenergic mechanisms the post synaptic nerve is cholinergic and causes the release of noradrenaline from peripheral stores. Thus the story of an action similar to acetyl choline or facilitation of acteyl choline would fit in well with this theory. On the other hand there is no direct proof that the implementation of acetyl choline action has any connection with the hypotensive action. Another possibility is that guanethidine has some action on the storage of catechol amines in the nerve ending. There is no proof that the mode of action is depression of conduction or interference in the synthesis of catechol amines.

Another hypotensive drug, Alpha methyl dopa, has been recently introduced. It has been shown to decrease the excretion products of tyrosine and tryptophane metabolism. It also reduces the stores of catechol amines in the heart and brain. It is thought that it acts as a competitive inhibitor of dopa decarboxylase and, hence, antagonises the formation of adrenaline and noradrenaline. However, after catechol amine depletion following alpha methyl dopa treatment the dopa decarboxylase activity has been shown to recover before the effects of the drug on blood pressure have worn off. Thus one has to postulate either a very slow turnover rate in the formation of the catechol amines, which seems most unlikely, or that competitive inhibition is only part of the story. Perhaps, as with reserpine, there is some interference with the storage mechanism.

BOOK REVIEW

THE CHILD AND HIS SYMPTOMS—A PSYCHOSOMATIC APPROACH by John Apley and Ronald MacKeith. published by Blackwell Scientific Publications, Oxford, at 25s.

"In illness the whole person is involved and, in trying to understand why he is ill at the time and in the way he is ill, it is logical to look at the whole person, body and mind. This is the comprehensive, psychosomatic approach."

Thus opens the preface of this book and thus it is well titled "The Child AND His Symptoms".

The reader must not be put off by regarding this book as only another esoteric account of the ins and outs of child psychiatry. On the contrary, Drs. Apley and MacKeith go to considerable length to put their "psychosomatic approach" into perspective with the simpler and more obvious diagnoses of organic disease.

As is implied by the title this book is mainly concerned with the common symptoms with which a child may present in the doctor's consulting room. Fourteen out of the twenty-three chapters are devoted to the discussion of one such symptom or group of symptoms, topics covered range from respiratory symptoms and recurrent pain to tics and feeding disorders. The two opening chapters are introductory and briefly explain what the authors mean by the term psychosomatic medicine. There are two excellent chapters on handicaps of various types and their effects on parent, sibling and child. The last four chapters are devoted to the discussion of the old subject of the doctor - patient relationship. There is nothing startlingly new in these chapters but there are several useful practical tips to be garnered.

The book is concisely written and is eminently readable to anyone remotely interested in paediatric medicine. The stress is naturally put upon the psychosomatic causes of symptoms but the authors back up their claims with brief, well chosen histories and some most interesting statistics. There are few illustrations, of any form, since these are hardly necessary. The book is well produced in a clear and simple fashion and includes a very adequate index and list of references.

Its price possibly places it outside the financial reach of the average student. However the time taken to read it would be well spent by anyone contemplating a career in general practice and certainly by the budding paediatrician.

N.A.B.

SOME NOTES ON THE PATHOLOGY AND THEORIES OF THE AETIOLOGY OF PRE-ECLAMPSIA AND ECLAMPSIA

From a Dissertation delivered to the Royal Medical Society
by R. Marshall.

Eclampsia and its precursor, pre-eclampsia, is an interesting and puzzling disease: for decades past, a great deal of study has been devoted to it, and yet its cause is still uncertain. This article attempts to summarise the features of the disease, together with some of the theories that have been submitted as to its actiology.

CLINICAL FEATURES

The classical clinical features are too well-known to need much description. Pre-eclampsia is characterised by hypertension, oedema and proteinuria, or a combination of these, appearing in the second half of pregnancy without any other obvious cause such as kidney disease. The state of eclampsia is said to be reached when convulsions and coma supervene, but so far as can be discerned by microscopic examination of the affected organs or by any other means, there is no other difference between pre-eclampsia and eclampsia: they are different stages in the same disease. For convenience, therefore, the term "toxaemia" will be used throughout the rest of this paper to mean pre-eclampsia and eclampsia together, although this is *not* the standard, accepted, nomeclature.

Certain other signs and symptoms may be present, including visual disturbances and retinopathy, oligura, pulmonary oedema, cyanosis and cerebral disturbances.

Retinal changes are a very constant and important finding in both pre-eclampsia and eclampsia. Constriction of the lumen of the arterioles is the first change seen: it may be either localised, giving a linked-sausage appearance to the vessel, or long and spindle-shaped.

Less constantly, papilloedema may occur, and in some severe cases retinal detachment.

As a rule there is marked improvement after the birth of the child, or after its death in utero. Proteinuria and oedema vanish within 4 or 5 days, and hypertension is usually gone after a fortnight.

PATHOLOGICAL HISTOLOGY

(a) *Liver.* On gross examination, irregular, reddish areas of haemorrhage are seen beneath the capsule and on the cut surface. The organ looks mottled.

Microscopically, peripheral haemorrhagic necrosis of the lobule is seen associated with extensive thrombosis in the small vessels in the periportal

connective tissue. It has been suggested that extravasated blood or plasma finds its way into the peripheral bases of the columns of liver cells, and causes them to be pushed up inside their surrounding "tubes" or "sleeves" of connective tissue.

At the bases of the columns, fibrin masses form, distending the sleeves and so compressing the blood sinuses. Large deposits of fibrin are characteristic of these lesions, which have a focal distribution.

The liver lesions are characteristic of toxaemia, but vary very much in extent and severity. Both autopsy and biopsy studies have shown that the degree of liver involvement is not related to the clinical severity of the disease.

(b) *Kidney.*

Three characteristic abnormalities are found :

(1) Swelling of the glomerular endothelial cells.

(2) Deposition of amorphous material against the normal basement membrane by the endothelial cells. (Formerly, before the use of the electron microscope, it was thought that the basement membrane itself was thickened).

(3) An increase in the number of intercapillary cells between the capillary loops.

All of these reduce the capillary lumens, and may account for the fall in glomerular filtration rate that is a feature of this disease. The glomeruli are usually all enlarged, by about 20%, and the outside diameter of the capillary loops varies from less than normal to about twice as big as normal.

Lesions are also seen in the tubules, but probably only represent congestion of the cells with protein reabsorbed from the glomerular filtrate. There are often casts, both of protein and haemoglobin derivatives, in the collecting tubules.

Rarely, thrombosis of the intralobular arteries may lead to complete bilateral cortical necrosis. This may be due to renal artery spasm, causing thrombosis and anaemic infarcts.

(c) *Brain*

In fatal eclampsia, involvement of the brain is likely. This may take the form of oedema, hyperaemia, anaemia, thrombosis or haemorrhage. Thrombosis of small cerebral vessels is common. Haemorrhage may range from small petechiae to massive bleeding, and is often associated with arteritis or arteriolitis.

(d) *Heart*

The heart is involved in most fatal cases, haemorrhages and areas of necrosis being found in the myocardium.

(e) *Lungs*

Pulmonary oedema is usually present. About 50% of cases coming to post-mortem have evidence of aspiration pneumonia, and some have lung abscesses.

(f) *Adrenals*

The adrenal glands are sometimes damaged, with a necrotic and haemorrhagic appearance. When this happens, nearly all the cortical tissue is usually destroyed, and adrenal insufficiency is probably a terminal factor in some cases of eclampsia. The adrenals are affected in an extraordinarily "all-or-none" sort of fashion: minor lesions are not seen.

(g) *Placental Changes*

In normal full-term placentae the incidence of "infarcts" is about 60%. This is raised in toxaemia, and is thought to indicate premature ageing of the organ. Some syncytial degeneration is characteristic of the normal placenta

at term, but only 10 - 50% of the small terminal villi are affected. All of them may be affected in toxaemia.

In the first stage of syncytial degeneration, clumping and autolysis of nuclei in the cytoplasm are seen, leaving clumps of dark-staining masses without cell outlines or nuclei. Later, all nuclei disappear from the syncytial layer, leaving the villi surrounded by a thin layer of hyaline material.

There is thus a great variety of clinical and pathological manifestations of this disease. They occur together so often, clearly as part of the same syndrome, that it seems reasonable to suspect that one pathological mechanism may be common to them all.

Now one common and constant observation in toxaemia is vasospasm; this may be seen directly in the ocular fundi, the nail beds, and the conjunctivae, and can account for most of the changes observed. Being widespread, it can of itself account for the hypertension. It may cause focal areas of hypoxia in the different organs. Circulation in the vasa vasorum is probably disturbed, causing damage to the vessel walls. The haemorrhages, necroses, and most of the other pathological changes can thus be explained by this one underlying condition.

Disorders of Function

Again, vasospasm can account for most of the disorders of function found in toxaemia.

It is well-known that constriction of renal blood-flow causes immediate proteinuria: it has been suggested that there are "leaks" in the glomerular capillaries due to transient hypoxia. Some authorities have suggested that there is a generalised disturbance of capillary permeability, of which albuminuria is a local renal manifestation. This would directly account for the generalised oedema. Eclamptic convulsions may be due to cerebral hypoxia, or cerebral oedema, or a combination of the two.

But vasospasm, although it satisfactorily explains most of the clinical and pathological phenomena of pre-eclampsia and eclampsia, is not the answer to all the mysteries of this disease. It must itself be caused by something—and its cause remains in doubt.

Biochemically, the classical feature of toxaemia is the excessive retention of salt and water. This is the basis for the usual treatment of pre-eclampsia with a low-sodium diet, with or without a diuretic; such treatment has excellent results in improving oedema. The ability of the kidney to concentrate sodium chloride is impaired in pregnancy, a feature that is exaggerated in toxaemia. Salt tolerance tests on mild pre-eclamptics have suggested that most (80%) are worsened by large doses.

Why salt and water should be retained is not fully understood. The sex steroids help to bring about retention of salt and water in normal pregnancy, but they are found to be decreased in the early stages of pre-eclampsia. Modern methods of assay have failed to implicate pituitary ADH; and while aldosterone may possibly be the cause of sodium retention it cannot be shown to be the primary factor.

Other biochemical changes in severe toxaemia include haemoconcentration (serum proteins, haematocrit and haemoglobin all rise as a result in decrease in the plasma volume), and in eclampsia, acidosis. The latter is due to a build-up of lactic acid and other acid metabolites during the muscular exertion of the convulsions.

Aetiology

First let it be said that most authorities credit toxaemia with being an independent entity, as opposed to the mere unmasking of such inherent traits

as essential hypertension. On this assumption, many hypothesis have been advanced to account for it.

To be satisfactory, any theory must explain certain observed facts, of which these are a few :

(1) The predisposing influence of primiparity, multiple pregnancy, hydatidiforin mole, and (perhaps) hydraminios.

(2) The disease is commoner in certain localities and in the lower social classes.*

(3) The increasing incidence as term approaches.

(4) Repeated eclampsia is rare.

(5) The classical signs and accompaniments of toxaemia.

(6) Improvement after the birth of the child, or its death in utero—although post-partum eclampsia may occur.

(7) The virtual elimination of the severer forms by good ante-natal care.

(8) The fact that pre-eclampsia and eclampsia are peculiar to pregnancy.

The earliest explanations of eclampsia, were on mechanical grounds, and may at once be dismissed. There was thought to be an increased intra-abdominal pressure that damaged the kidneys by compression of the renal vessels and ureters.

Many toxins have been suspected as the cause of pre-eclampsia and eclampsia—hence the name "toxaemia"—including urea, ammonium carbonate, carbanic acid, creatine and creatinine, besides many more. Against all of these is the fact that blood from toxaemic patients has no effect when transfused into normal pregnant women; however, some workers have suggested that the trouble lies in the absence of antitoxins to counteract *normally-present toxins*, but none of the substances named above can be shown to be the cause of this disease.

Other early theories incriminated infection, which is not acceptable, and foetal metabolic products. The latter cannot be the cause, for toxaemia can occur with hydatidiform mole. Another early hypothesis, that toxaemia is brought about by incompatibility between maternal and foetal blood, can very easily be shown to be incorrect.

Among contemporary hypotheses, Sophian *et al.* have presented a theory based on the "Trueta shunt mechanism", postulating a utero-renal reflex whereby sudden distension of the uterus causes a diversion of the blood-supply from the cortex to the medulla of the kidney. While this would no doubt account for many of the observed phenomena of pre-eclampsia and eclampsia, it cannot be shown that the Trueta Shunt in fact occurs in the human kidney. However, this theory still has many agonists.

As the placenta is a complicated organ that we still have much to learn about, it is hardly surprising that many workers have sought, and are seeking, a cause for toxaemia there. It has not been possible to incriminate a placental endotoxin, because although syncytial cells can become detached and enter the maternal bloodstream, deposits of these have been found at post mortem in the organs of women dying for other reasons, who had not had toxaemia.

The so-called placental "infarcts" have been incriminated as the source of toxins by some workers, who take the view that in the "red infarct" stage these lesions are proteolysed, and that their products, which are partly absorbable, are nephrotoxic. They are not in fact infarcts at all, being merely signs of senescence of the placenta, and are present in about 60% of all cases. Whether the extent of infarction and the severity of toxaemia are at all related is still a matter of considerable controversy; and the incidence of toxaemia with hydatidiform mole, where infarcts are not found, is evidence

* Footnote.—This may be due to variation in antepartum care.

against this theory. It seems more probable that infarcts are an effect rather than a cause of toxaemia.

The most widely-held theory at the present time is that of Uterine Ischaemia. This postulates that in an ischaemic state of the uterus, a placental or decidual substance with hypertensive properties is released in much the same way that an ischaemic kidney produces renin. What such a substance might be is not known, but histamine has been suggested, and more recently Hunter and Howard have reported the presence of a pressor polypeptide, "hysterotonin", in the decidua and amniotic fluid of toxaemic women. They find that plasma and decidual extract from patients with pre-eclampsia or mole cause contraction of smooth muscle, and have a pressor effect on the pithed cat. Again, Sandler & Coveney have suggested that placental monoamine oxidase activity may be diminished in toxaemia, with the resulting reduction of inactivation of endogenous amines leading to vasopasm and anoxia.

This theory fits many of the facts :

(1) In primigravidae, the uterine vessels have not undergone hypertrophy. Also there is greater tone in the abdominal wall, possibly causing pressure on the uterus.

(2) Multiple pregnancy and mole—excessive or sudden expansion of the uterus might make it outgrow its blood-supply.

(3) Aggravation of pre-eclampsia in labour—there is uterine ischaemia with the contractions.

(4) The increased incidence as term approaches.

(5) The characteristic liver lesions, which are explained in this way: the placenta is the richest source of thrombaplastin in the body, and if it were injured by ischaemia it would very probably suffer cytolysis of the syncytial epithelium, allowing the entry of thromboplastin into the maternal circulation. There, it might conceivably contribute to the large deposition of fibrin seen in the liver lesions.

This is probably the most widely-held theory at the moment, as was remarked above. Why uterine ischaemia should occur in some women and not others, aside from any of the predisposing factors such as multiple pregnancy, etc., is not clear: it is suggested that they have a pre-existing hypoplasia of the uterine vasculature, but this is not universally accepted.

Other theories have suggested that toxaemia was purely an endocrine disorder. It has been ascribed to thyroid malfunction, which can be swiftly dismissed, to hyperfunction of the posterior pituitary, which there is little evidence to support, and to hyperfunction of the adrenal cortex. Pregnant women are thought to produce more corticosteroids in the last trimester than non-pregnant women: some workers hold the view that in patients with pre-eclampsia or eclampsia a poorly-functioning placenta fails to inactivate these hormones. Variations are also noted in the amounts of oestrogen, progesterone, and chorionic gonadatrophin produced in toxaemic patients, but no endocrine disturbance can be shown to be a primary cause of the disease.

Mention must be made of the nutritional theories. Theobald has pointed out that many bizarre and unfamiliar syndromes may result from deficency of particular food factors or groups of food factors, as was demonstrated vividly in Japanese prisoner-of-war camps in the last war, for example. Dietetics is a subject of great complexity, and is not yet fully understood: it is possible

to live on far less than the "standard" requirements, but in such circumstances a variety of pathological phenomena are liable to become evident. It seems not unreasonable to suppose that the enormous metabolic task of producing a full-term infant might create a deficiency of certain dietary constituents in a woman who is very well fed by ordinary standards: it also seems fair to suppose that some women may have inborn metabolic idiosyncrasies which make such a task much more difficult for them than for others. Might such a deficiency manifest itself as pre-eclampsia or eclampsia?

Oedema can be produced, in a little-understood way, by malnutrition. Liver damage can result from the absence of certain amino acids. A lack of vitamin B can cause ovarian disfunction, and as ovarian hormones are needed for the successful implantation of the placenta, the premature senility of that organ may be the result of a degree of malnutrition. (It is of interest that Dalton has had good results from giving prophylactic progesterone in early pregnancy, before pre-eclampsia has become established.) Theobald considers that convulsions may be caused by cerebral oedema, changes in the Ca/Mg ratio, a sudden slight fall in the blood sugar, or electrolyte inbalance—all possible consequences of malnutrition.

But what of hypertension? Theobald considers this to be no more than a red herring in pre-eclampsia and eclampsia, claiming that when it is found in pregnancy it is merely the result of an underlying essential hypertension.

The obvious argument against this theory is that, if pre-eclampsia and eclampsia are evidence of a dietary deficiency disease, why should non-pregnant women—or even men—be immune? Presumably the other special circumstances of pregnancy—hormonal, mechanical, etc.—might be such that this syndrome can only manifest itself in such women.

Certainly this is a very interesting theory, and one that cannot be lightly dismissed.

Present methods of treating pre-eclampsia and eclampsia, although very successful as a rule, are quite empirical. It is to be hoped that eventually the mysteries of this disease will be solved, and that a more specific line of treatment or prevention will become available. Then, perhaps, this common and serious hazard of pregnancy will at last be overcome.