Current Practice

TODAY'S DRUGS

With the help of expert contributors we print in this section notes on drugs in current use.

Aspirin and Alternatives

Willow-bark, which contains salicin, is said to have been used by Hippocrates as a bitter, but the isolation and therapeutic effects of salicylate were not realized until the last century when its antipyretic, analgesic, and uricosuric actions were discovered. Several variants of the salicylate molecule are pharmacologically active. Aspirin, or acetylsalicylic acid, was introduced in 1899 in the hope that it would prove more acceptable from the point of view of therapeutic efficacy, taste, and gastric irritation than salicylic acid or its sodium salt. It has remained by far the most popular form of salicylate.

Despite aspirin's pre-eminence as an analgesic many other salicylate preparations or special formulations of aspirin have been marketed in recent years as substitutes for plain aspirin. The two main objectives have been improvement in rate of absorption and elimination, thereby enhancing the analgesic effect, and avoidance of side effects, particularly dyspepsia and gastrointestinal blood loss. In addition, aspirin and other forms of salicylate are incorporated in many compound preparations. Quite apart from those advertised to the public, there are 45 such special or compound formulations listed in the current Monthly Index of Medical Specialties.

Absorption and Excretion

Aspirin is poorly soluble in acid or neutral solution but is readily absorbed from the gastrointestinal tract, mainly by passive diffusion of the undissociated molecule across the wall of the gut. The diffusion rate is influenced by many factors, including the concentration of the un-ionized drug and hence the pH at the mucosal surface, the viscosity of gastrointestinal fluids, the gastric emptying time, and the tablet dissolution time; the last in turn varies with the physicochemical properties of different brands of tablet. It is the dissolution rate (the rate at which a particular preparation of aspirin goes into solution) rather than the disintegration time of the tablet which is the rate-limiting step in the absorption of most aspirin preparations. Blood salicylate levels are higher if aspirin is dissolved in warm water or alkali before ingestion. The effect is similar with effervescent preparations, which consist of dry mixtures of aspirin with alkalis such as sodium citrate, sodium bicarbonate, or calcium carbonate; aspirin buffered with glycline is also probably more rapidly absorbed. However, no better analgesic effect has been demonstrated with consistency, and from the practical point of view any improvement is probably marginal and unimportant.

In the blood 50%-80% of salicylate is bound to plasma protein. Almost all is eliminated in the urine within 48 hours, excretion being influenced by glomerular filtration rate, tubular secretion, urine flow, and pH. If the tubular urine is acid most of the filtered salicylate, being un-ionized, is readily reabsorbed, but in alkaline urine the ionized salicylate is only slightly reabsorbed. Simultaneous administration of sodium bicarbonate therefore hastens elimination of free salicylate, and it is owing to this that bicarbonate diminishes the toxicity of salicylates. There is therefore no point in prescribing the two drugs together, as was formerly the practice.

Pharmacological Actions

Salicylates are analgesic, antipyretic, and anti-inflammatory. The analgesic effect has been considered to be predominantly one of selective depression of the central nervous system, but the mechanism and exact site of action remain to be determined. A peripheral effect has also been shown in animals and also in man on visceral pain induced by injection of bradykinin. Pain of moderate severity arising from skeletal or integumentary structures tends to be relieved by salicylate, rather than severe pain of visceral origin, and aspirin finds its widest use in pain arising from joints and muscles, as well as headache and toothache.

The antipyretic action is usually rapid and effective, heat dissipation in febrile patients being augmented by increased peripheral blood flow and sweating. Salicylates and other antipyretics produce their effect mainly through the central nervous system rather than by a peripheral action on blood vessels or sweat glands, and it can be abolished in animals by high section of the spinal cord. Though salicylates lower a raised body temperature they increase oxygen consumption and metabolic rate, and so in toxic doses produce pyrexia with sweating and dehydration.

The anti-inflammatory properties of salicylates can be shown in experiments on animals and in man, where, for example, large doses reduce joint inflammation as well as easing pain and stiffness. Other inflammatory lesions can also be suppressed, such as the oedema and erythema of the skin which is evoked by thurlf nicotine; in this situation aspirin is very potent whereas sodium salicylate has no appreciable effect. Again, the mechanisms concerned are largely unknown. The possibility of interference with the venous media tor systems which lead to increased capillary permeability and inflammation exudation—kinins, histamine, 5-hydroxytryptamine, etc.—has been extensively investigated, but no clear picture emerges; and the suggestion that salicylates, like corticosteroids, directly stabilize lysosomal enzymes awaits confirmation. A vast amount of work has been carried out on the numerous metabolic effects of salicylate, but their relation to its therapeutic action remains quite obscure.

Salicylates are also powerful uricosuric agents, increasing the renal elimination of uric acid by suppression of tubular reabsorption. However, to achieve this it is necessary to maintain a plasma salicylate level of over 10 mg./100 ml., which usually means that high dosage (about 5 g. daily, or fifteen 325 mg. tablets) is necessary for consistent uricosuria. Lower doses are not only ineffective but have an opposite effect, causing retention of urate: salicylates also antagonize the action of other uricosuric drugs such as probenecid and sulphinpyrezone. For this reason and because of the availability of other highly effective drugs aspirin has no place in the treatment of acute or chronic gout.

Side Effects and Toxicity

Side effects of salicylates can be considered in three categories—those resulting from overdosage, those due to...
drug allergy, and those associated with therapeutic dosage continued over more or less prolonged periods.

Mild overdosage or "salicysm" is not uncommon during treatment of rheumatic diseases, with symptoms mainly referable to the nervous system—dizziness, faintness, weakness, and dullness in the head. These symptoms are quickly reversible as the drug is stopped. Severe intoxication is today rare in clinical usage, though it did occur, sometimes with fatal results, when salicylates were used in massive intravenous dosage for the treatment of rheumatic fever. The more serious effects of salicylate overdosage are nowadays much more often associated with accidental administration in children or suicidal attempts in adults, both of which are common, leading to approximately 3,000 admissions to hospital every year. Symptoms include vomiting, headache, visual impairment, sweating, flushing of the skin, perspiration, haemorrhage, and drowsiness leading to coma. Hyperventilation is a prominent sign of salicylate overdosage, the result of direct stimulation of the nervous system. Respiratory alkalosis is, however, only one of the complicated changes in acid-base balance which salicylates can produce, being seen predominantly in adults: in young children the first change is usually metabolic acidosis. It follows that the management of salicylate intoxication requires close biochemical control, and the importance of early hospital admission for suspected cases cannot be overemphasized.

Adverse reactions to small doses of salicylate have included urticaria, purpura, angioneurotic oedema, asthma, rhinitis, and anaphylactic shock, but such allergic reactions are rare. There is little correlation between aspirin sensitivity and the results of skin testing, but it is possible that lymphocyte transformation studies will come to offer a more reliable index of susceptibility.

In recent years increasing attention has been paid to the possibility of harm resulting from prolonged ingestion of salicylate, with particular reference to gastrointestinal and renal damage. Haemorrhage occurs with a frequency of about 25%. Though it is common to encounter patients who can tolerate modified preparations of aspirin better than the plain tablet it is not easy to be sure of the various parameters determining this preference. Such patients, for instance, will sometimes declare an aversion to one commercial brand of plain aspirin compared with another, unaware of their similar composition. Though buffered aspirin has been held to produce less dyspepsia controlled studies have failed to confirm this.

From direct observation of lesions in the stomach, and by detection of blood in gastric aspirate or stools of people taking aspirin, it has become evident that haemorrhagic erosion of the gastric mucosa is a normal response to salicylate. Quantitative estimation of faecal blood loss has shown that appreciable bleeding occurs in about 70% of subjects taking aspirin, but the quantity of blood loss is usually small, in the order of 5 ml daily.

Sometimes, however, chronic haemorrhage is of sufficient degree to produce anaemia, and the possibility must be remembered wherever a falling haemoglobin level is found in a patient on long-term salicylate therapy. The response of any one individual tends to be relatively constant and reproducible, and the presence of pernicous ulceration does not appear to increase the amount of blood loss. Chronic gastrointestinal haemorrhage occurs independently of dyspeptic symptoms, and swallowing tablets after meals causes as much bleeding as taking them on an empty stomach. Results of investigation into the capacity of various modifications of aspirin to produce gastrointestinal bleeding have not always agreed, but it appears that the effect also follows the ingestion of soluble aspirin, glycine aspirin, and aspirin anhydride. The incidence of bleeding is reduced by the use of enteric-coated preparations or aloxiprin (a polymer of aluminium oxide and aspirin), which pass through the stomach unchanged.

It is possible that salicylates are occasionally capable of producing a massive bleed, though evidence from retrospective clinical reports is difficult to evaluate because it is often uncertain to what extent the taking of aspirin is in fact responsible for the sequence of events. On the whole there have been a tendency to exaggerate these dangers, and the experience of those dealing with large numbers of patients with diseases such as rheumatoid arthritis indicates that these disadvantages are not sufficient to contraindicate careful clinical use.

Renal Damage

There is also considerable current interest in the question of analgesic tablets and chronic renal damage. Many reports have described the development of renal papillary necrosis and interstitial nephritis in people taking large quantities of analgesic mixtures containing phenacetin. A strong case has therefore been made for nephrotoxic properties of phenacetin. Since, however, aspirin is present in many compound analgesic tablets the opinion has been expressed that aspirin may be harmful rather than, or in addition to, phenacetin. It is true that renal failure can follow acute overdosage with salicylate and even small doses of the drug cause a brisk but transient exfoliation of renal tubular cells. However, aspirin has not always been included in the offending mixture and there have been no detailed reports of renal papillary necrosis attributable to aspirin alone, despite a general awareness of the problem. Animal experiments have failed to resolve the matter, and at present the evidence that prolonged administration of salicylate itself causes significant renal damage is unconvincing.

Salicylates have no effect on the normal heart, but in the presence of pre-existing heart disease they may occasionally precipitate pulmonary oedema or congestive heart failure owing to increased cardiac work and output. Salicylates are, therefore, potentially dangerous in patients with active rheumatic fever and cardiac enlargement: it is in this group that treatment with corticosteroid hormones is particularly indicated.

Therapeutic Use

The dose of aspirin depends to some extent on the condition being treated. As an occasional analgesic and antipyretic for the relief of headache, colds, toothache, and various forms of musculo-skeletal pain it is usual to give a single dose of 0.3 to 1.0 g. (1 to 3 tablets), repeated as necessary. In chronic rheumatoid arthritis relief of pain and stiffness by aspirin is important because proper exercises can then be carried out by the patient with consequent prevention of deformity and maintenance of function. A common error is to prescribe too small an amount of the drug: the correct dose is an individual matter, lying below that which produces anorexia and tinnitus but being sufficient to produce maximum pain relief. For an adult it usually amounts to 4-6 g. daily (12 to 18 tablets), given in four divided doses: the first dose should be taken immediately on waking so that morning stiffness is eased as rapidly as possible. The daily dosage for children is in the order of 150 mg./kg. daily: in young patients with rheumatic fever it is usual to check the blood salicylate level, which should lie between 20-30 mg./100 ml. It should be noted that though the response to pain and fever to salicylate in rheumatic fever is often striking it is by no means specific, and the oft-quoted notion that such a response is in some way diagnostic of the condition is quite erroneous. Full doses are continued in rheumatic fever until the patient has been asymptomatic (and preferably the E.S.R. normal) for about two weeks, when the drug is gradually discontinued: the danger of fluid retention has already been mentioned.
In most patients plain aspirin is as useful as any other preparation. Some patients prefer to take soluble aspirin (Disprin, Solprin) in water, or buffered preparations such as aspirin-glycine (Paynacol). Gastrointestinal bleeding and dyspepsia are lessened with enteric coated aspirin (Nuseal aspirin) and aluminium polyoxyoaspirin (Palaprin Forte), though it must be remembered that these preparations are much more expensive than plain aspirin. The formulation of glycin-aspirin, aluminium polyoxyoaspirin, and the larger preparation of enteric-coated aspirin in tablets of (approximately) 0.6 g, is an advantage, since fewer tablets have to be swallowed. The slow absorption of enteric-coated aspirin means that more sustained blood-levels are achieved, the maximum being at about eight hours after ingestion: an evening dose is therefore effective early the following morning, which is sometimes helpful in alleviating the morning stiffness of rheumatoid arthritis.

**Alternative Analgesics**

Phenacetic is a weak analgesic which frequently causes enterogenous cyanosis due to the formation of methaemoglobin, and almost certainly produces chronic renal disease when taken in large quantities over a prolonged period. Though the drug remains available for prescription either alone or in tab. codeine co. (B.P.), it is more than doubtful if it should ever be used. It has been withdrawn from ‘Codis’ and ‘Veganin’ compound tablets. Paracetamol is a metabolite of phenacetin and, though also a weak analgesic, appears to be safe, lacking as far as is known the adverse properties of its precursor. Patients can take 6 to 10 0.5-g. tablets daily, and the drug is commonly used as an alternative to aspirin. Codeine phosphate is another alternative analgesic: a dose of 30 mg. is said to be equivalent in analgesic effect to 600 mg. of aspirin with a supra-additive effect when the two drugs are combined. Codeine is constipating, however, and not often suitable for long-term analgesia on its own. Dihydrocodeine tartrate (D.F. 118), in 30 mg. tablets, is also an effective and safe mild analgesic.

A large number of compound proprietary analgesic preparations are marketed, consisting usually of aspirin, phenacetin, or paracetamol in association with tranquillizers, sedatives, stimulants, relaxents, vitamins, and other analgesic substances such as salicylamide, dextropropoxyphene, and ethophetazine. Assessment of such a wide range of preparations is not easy, but in general, if two or more drugs are necessary, it is better to prescribe them separately rather than in a fixed-ratio compound tablet. None of these tablets appears to be of any special value.

**ANY QUESTIONS?**

We publish below a selection of questions and answers of general interest.

**Relief of Priapism**

Q.—A middle-aged man with peripheral neuritis has distressing priapism. He has sensory loss in the penis, and it is apparently impossible to produce an emission by tactile or other stimulation. Could some form of stimulation of the autonomic nervous system relieve him?

A.—Priapism occurs occasionally in a variety of neurological lesions, including multiple sclerosis, tabes dorsalis, spinal cord lesions at any level, and encephalitis. It is not clear whether the patient referred to hopes for relief by some form of stimulation of the autonomic nervous system to produce emission.

The sympathetic nervous system is concerned in emission, but it is unlikely that the patient can be helped with a sympathomimetic drug. Various methods of treating priapism have been discussed. In this case interruption of the parasympathetic supply in the neri erigentes—at first by injection and later, if successful, possibly surgically—might be helpful.

**REFERENCES**

1 Oldfield, J., British Medical Journal, 1959, 2, 1227.

**Uterine Bleeding and Fetal Defects**

Q.—What is the current opinion on bleeding during the first half of pregnancy as a significant intrauterine cause of congenital defects?

A.—Javert in a large series found that the incidence of spontaneous abortion was 8.3%. One-third approximately of all these abortions were threatened only. Others seem to agree that threatened abortion is found in not more than 5% of all pregnancies. Of his spontaneous abortions, Javert found that 35% showed abnormalities. Therefore it is concluded that abnormalities of the ovotetus are a major cause of abortion. This is confirmed by the fact that at term the fetus is moderately or grossly abnormal in 1-5 to 2% of cases. Burge in 289 cases of fetal abortion found the threatened abortion rate in these pregnancies was 8%, being about the same as in pregnancies where the baby was normal at birth.

The figures seem to suggest that bleeding is probably not a cause of fetal abnormality, but that fetal abnormality is a cause of abortion. However, bleeding in early pregnancy is evidence of some disturbance of embedding of the trophoblast and, if the bleeding occurs after about the sixteenth week of disturbance of the placenta, since the placenta forms as a disc at about this time, it would seem possible therefore that such disturbance might impair the nutrition of the embryo or fetus and cause it to develop abnormally. But it is believed that congenital anomalies arise as a result of imperfect differentiation, which is virtually complete at 12 to 14 weeks of pregnancy. Even this belief is called into question by the evidence that rubella contracted in later pregnancy may cause congenital defects. Also the incidence of fetal abnormality in cases where the placenta is praevia is higher (9.2% as against 3.2% where the placenta was normally situated), suggesting the possibility that the placenta may determine the changes in the baby. But it is possible that any abnormality of the fetus may determine the site of its placenta, since some believe that if the egg is fertilized after some delay there may be a higher incidence of placenta praevia.

The question cannot be answered unequivocally, except to say that there is no firm evidence that bleeding in early pregnancy is a cause of congenital defects. This does not mean of course that such bleeding has no significance, for the perinatal mortality survey showed that the chances of perinatal death when there had been a threatened abortion was nearly two-and-a-half times as high when there had been no bleeding in early pregnancy.

**BIBLIOGRAPHY**


**REFERENCES**

3 Burge, E. S., American Journal of Obstetrics and Gynecology, 1951, 61, 615.