Renal Vascular Damage after Birth

In the neonatal period the kidney seems unusually prone to vascular damage from thrombosis, embolism, or ischaemic necrosis. The factors responsible for this susceptibility include the small calibre of the renal vessels, the low renal blood flow, the rapid rate of fluid turnover, and the relative polycythaemia of the newborn period. In addition there are specific causes including perinatal asphyxia, birth trauma, blood loss, saline depletion or hyperosmolar dehydration following diarrhoea, septicemia with disseminated intravascular coagulation, cyanotic heart disease, radiological studies utilizing contrast media, and maternal diabetes.

The most common form of vascular abnormality is renal venous thrombosis (the preferred terminology for the usual site of the thrombosis) in the arcuate or interlobar veins with extension to the cortex or to the intralobular and main renal veins. Unilateral and bilateral cases occur with equal frequency, usually in the first week of life, but a recent European survey showed that nearly half the cases were discovered only at necropsy, suggesting the need for greater awareness of conditions predisposing to the condition and of its clinical features. Haematuria and enlarged palpable kidneys are found in more than half the cases, but absence of these signs does not preclude the diagnosis: oliguria, ureaemia, metabolic acidosis, proteinuria, anaemia, and thrombocytopenia may be present. The last two findings suggest the possibility of a consumptive coagulopathy and microangiopathic haemolytic anaemia as a secondary or even predisposing phenomenon to the venous thrombosis.

Oedema and cyanosis of the legs may be found if there is thrombosis of the inferior vena cava. Intravenous urography is the most useful investigation, but it should be postponed until the clinical condition has improved after appropriate resuscitation. It is better undertaken by units with special experience of renal radiography in this age group, for it is not without risk, and the interpretation may be difficult. The finding of an enlarged, poorly functioning kidney with no pelvicicalical dilatation sustains the clinical diagnosis, but if a nonfunctioning kidney is present then further investigations such as nephrophonography, antegrade pyelography, or retrograde pyelography may be required to exclude renal agenesis, cystic dysplasia, or hydronephrosis. Final confirmation, especially in bilateral cases, requires inferior vena caval and selective renal vein venography, but the risks deter most paediatricians unless thrombectomy is contemplated.

Reports that the condition is invariably fatal must now be revised: over one third of the children reported in the European survey survived in good health. Conservative management includes peritoneal dialysis where necessary. Heparin anticoagulation is commonly used, especially where consumptive coagulopathy coexists, though no controlled trial has been reported to justify it and recovery is possible without heparin, even in bilateral cases. Thrombectomy for bilateral cases with vena caval thrombosis has been successful, but again the treatment is controversial. For the present it seems reasonable not to commend thrombectomy until an adequate trial has been concluded, though such a study would require co-operation between a number of centres.

The recognition of survivors has led to reports of late sequelae; hypertension may appear some months later, and possibly non-functioning kidneys should be removed, after the acute stage but before hypertension develops. Other sequelae include the nephrotic syndrome, while recently multiple renal tubular abnormalities were found in three children who had evidence of neonatal renal venous thrombosis. One of the children had a classical Fanconi syndrome; it seems that renal vascular accidents must now be added to the list of acquired and congenital causes of this syndrome.

Adrenal haemorrhage is uncommon, but when it occurs it may be confused with renal venous thrombosis. The onset is sudden with pallor, lethargy, and shock; a large mass is often palpable in the loin and there may be blood-stained ascites. Oliguria, proteinuria, and microscopic haematuria occur, and intravenous urography shows the kidney displaced downwards with compression of upper pole calices. The haemorrhage rapidly calcifies, and this can be noted on plain radiographs 2–4 weeks later. Temporary adrenal insufficiency may be found in bilateral cases. Renal arterial thrombosis is rare and usually secondary to embolism from bacterial endocarditis; it may be an incidental complication of congenital heart disease, umbilical arterial catheterization, or renal venous thrombosis. The diagnosis is difficult, but evidence of arterial thrombosis remote from the kidneys should be sought.

Severe cases of acute tubular necrosis may be accompanied by papillary necrosis and again the precipitating factors are similar to those in renal venous thrombosis. Late effects...
Drugs for Prevention of Malaria

Two recent reviews of the problem of imported malaria in Europe\(^1\) and in the United Kingdom\(^2\) have shown the shortcomings in the use of available prophylactic drugs. These are due partly to the spread of resistance of human plasmodia to the present compounds. As pointed out\(^3\) by Peters, the question: "Doctor, what drug should I take against malaria?" can be rather perplexing. Much of this uncertainty is caused by lack of information on the response of various species and strains of malaria parasites to commonly used chemoprophylactic agents.

Widespread drug resistance is a serious problem mainly with regard to *Plasmodium falciparum*. Although some strains of *P. vivax* and *P. malariae* do not respond fully to prophylactic drugs such as proguanil or pyrimethamine or to standard treatment with quinine or primaquine, these findings are of limited importance in comparison with the extent and degree of resistance of tropical *P. falciparum* to various antimalarials including chloroquine and amodiaquine—hitherto our best available compounds. However, these problems of treatment of drug-resistant *P. falciparum* have been partially solved by renewed evidence of the therapeutic virtues of quinine and by the discovery of the synergistic action of antifolic drugs (pyrimethamine, trimethoprim) with long-acting sulphonamides (sulphadoxine, sulphalcene, and others). Moreover a series of new antimalarial compounds (9-phenanthrene methanols, 4-quinoline methanols, and others) has been assessed in experiments on monkeys in the U.S.A. and may soon become available.\(^4\) \(^5\) The question of individual prevention of malaria in travelers and expatriates living in tropical areas can be answered only in general terms. Proper selection of the best prophylactic compound depends on knowledge of the characteristic of malaria in the given area (including the pattern of drug response) and other factors, such as convenience, individual tolerance, and last but not least local medical experience. Regular drug taking is of paramount importance, yet probably only about half of travellers take any prophylactics while in the tropics and only 20% take them for one month after returning from abroad.

Proguanil and pyrimethamine are still the best all-round truly prophylactic drugs. Many experienced observers prefer proguanil taken daily at a dose of 100-200 mg to pyrimethamine taken once a week at 25-50 mg, because the daily regimen offers a better chance of maintaining a regular intake. These two antifolic drugs have a similar effect on the pre-erythrocytic forms of human plasmodia and especially *P. falciparum*.

There are, however, undoubtedly areas of the world where *P. falciparum* is resistant to pyrimethamine. This applies particularly to East Africa and South-East Asia, and there is good evidence that resistance is also present in many parts of West Africa. Clearly, this limits the causal prophylactic value of this compound and may call for its substitution or reinforcement by another compound such as chloroquine.

Because of their closely related antiplasmodial action, resistance to pyrimethamine is usually linked with cross-resistance to proguanil. This is not always true, however, and proguanil at the normal or double (200 mg daily) dosage may still give a reasonably good protective effect in areas of pyrimethamine resistance.\(^6\) \(^7\)

Of the two widely used 4-aminoquinolines chloroquine was the most dependable suppressive drug until the appearance of resistance to it nearly 15 years ago. With the exception of areas of confirmed altered response of *P. falciparum* to 4-aminoquinolines in South-East Asia and in parts of South America and Central America, there is good evidence that chloroquine and amodiaquine are still the most reliable drugs for suppression of malaria and for its treatment.\(^5\) \(^7\)

So far there is no evidence of resistance to chloroquine in Africa, in Asia west of Burma, or in the West Pacific.\(^4\) The view held by some that the prophylactic use of chloroquine leads to the development of resistance of *P. falciparum* to 4-aminoquinolines cannot be justified by any experimental or epidemiological evidence. Less controversial are the differences between the usual dosage of prophylactic chloroquine in French-speaking parts of Africa (where 600-700 mg of chloroquine base is given over the week) compared with the generally advocated regimen of 300 mg base in English-speaking African and other countries. It is probable that the "French regimen" gives a better degree of protection though it may also cause some side effects. Pregnancy is not a contraindication to the use of antimalarial drugs at the proper dosage.

Resistance of *P. falciparum* to chloroquine often extends to amodiaquine, but the latter compound may still be effective when chloroquine fails.\(^9\) The same can be said about quinine, though its prophylactic use cannot be recommended for many other reasons.

Since the entry of sulphonamides and sulphones into the category of antimalarial drugs the question of their use for prevention of the infection has been debated with more heat than light. Combination of a standard proguanil regimen with the addition of daily dapsone (25 mg) during the peak transmission of malaria has been successful in groups of non-immunes in South Vietnam. An association of pyrimethamine (12-5 mg) with dapsone (100 mg) given once a week