nine. The secretion of thyroxine (T-4) is normal, though later it may become excessive. It is thought that this disordered pattern of secretion may be due, in some cases at least, to iodine deficiency. The patient is clinically thyrotoxic, but the conventional tests of thyroid function are normal. A firm diagnosis can be made only by direct measurement of T-3 and T-4 in the plasma. These techniques are not yet generally available, but a failure to suppress uptake of iodine-131 by the T-3 test will support the diagnosis.

1 Davies, A G., British Medical Journal, 1972, 2, 206.
2 Hollander, C. S., and Shinkman, L., British Journal of Hospital Medicine, 1972, 5, 393.
4 Burke, G., American Journal of Medicine, 1967, 42, 600.

Profits from Drugs

Critics of the pharmaceutical industry have been given fresh ammunition by the publication of the report1 of the Monopolies Commission on Roche Products' tranquillisers chlordiazepoxide and diazepam (see p. 189). The commission found that the level of the company's profits had been "unjustifiable" and the Government is to use its powers under the monopolies legislation to compel the company to cut its prices.

The relationship between the Department of Health in its role as customer and the pharmaceutical industry has never been easy. Under the Voluntary Price Regulation Scheme the Department negotiates drug price levels with the manufacturers, and the scheme requires the submission of annual financial returns by the companies to provide a basis for agreement on the reasonableness of profits. Roche Products has always declined to take part in the voluntary scheme, and indeed has argued that the scheme is a form of excess profits tax. Though it had negotiated some repayments to the Department in the late 1960s, the company has refused to discuss prices since 1970. This attitude seems to have been a reaction to the Government's use of powers to grant compulsory licences to other firms to manufacture and sell drugs on which Roche held patents. The Department had, in the company's view, created conditions which made negotiations impossible, and this impasse led to the reference to the Monopolies Commission. The Roche parent company based in Switzerland refused to give the Monopolies Commission information on its world-wide sales and research costs, so that the commission's figure for the profits from the sale of the two drugs in the United Kingdom of £25 million over seven years is its own estimate. Roche claims that its prices in Britain are only half the world average prices for its drugs, but the commission argues that the company nevertheless makes higher profits than do comparable British-based firms.

What is not disputed is that Roche has an outstanding record of production of drugs valuable to medicine. The safety and freedom from side effects of the benzodiazepine tranquillisers have made it possible for doctors to stop prescribing barbiturates for many indications. More recently Roche has pioneered production of levodopa despite the lack of patent protection. If the company's profits have been high at least its research has been productive. Indeed Roche claims that it has never paid more than 2% of its turnover to its shareholders, the bulk of its profit being reinvested in long-term research.

Clearly it is reasonable for a Government to try to keep down the prices paid by the N.H.S. for its drugs; but there are now three ways in which it can interfere with the operation of normal market forces. The voluntary pricing scheme allows the Government to assess what are "reasonable" profits; the patents legislation allows the Government to grant licences to rival manufacturers to compete with the firm that developed a drug; and now the Roche incident has shown that if the Government is still dissatisfied it can in certain circumstances go to the Monopolies Commission for a recommendation for compulsory price cuts. This complex system of restraints is likely to cause ill-feeling within the pharmaceutical industry, which is heavily dominated by international companies. For these foreign-based firms the British market represents a very small proportion of their activities, and it would be unfortunate if relations between them and the Department of Health deteriorated. The present system of price control is clearly cumbersome and some companies at least resent the Government's intrusion into their internal financial affairs. There is no easy compromise between the view that "excess" profits should not be made out of illness and the free enterprise attitude that argues that prices and profits should be determined by what the market will bear. If either Government or industry pushes too hard the result could be disastrous for pharmaceutical research in Britain. Perhaps the time has come to take another look at the arrangements for determining drug prices in an attempt to find a more acceptable system.


Gallstone Composition

The introduction of new analytical techniques has provided interesting information about the composition of gallstones. A quantitative microanalytical method has been recommended1 but in Britain much of the new information derives from the work of June Sutor and her colleagues, who rely on x-ray diffraction technique. This identifies the crystalline substances in a gallstone,2 but the method has the disadvantage that amorphous material such as bile pigment and glycoprotein cannot be identified.

The main component in gallstones from the western hemisphere is cholesterol, though other crystalline compounds can be identified, among them calcium carbonate, calcium phosphate, and calcium palmitate.3 It is only since 1970 that calcium palmitate has been recognized as a component of gallstones other than from Japan.4 Indeed it is the fourth most abundant compound in stones from patients in the West.3 In a recent study of 31 patients A. G. A. Cowie and his colleagues found two patients who harboured pure calcium palmitate stones, but such stones must be regarded as rare, amounting to between 0·02 and 0·07% of all gallstones studied.3 5

An awareness of the precise chemical composition of gallstones will lead to a more accurate classification. In addition it is possible that this knowledge could provide an answer to
at least three questions: do stones of differing composition cause different symptoms: does the composition of the stone reflect metabolic events at the time of its formation; and does the composition predict whether the stone is likely to respond to medical treatment? Though Cowie and colleagues suggest that pure calcium palmitate stones might be associated with a particular clinical situation, they agree that this is speculation. Other studies indicate that symptomatology is necessarily related to the composition of the stone, though it should be recalled that pigment stones are frequently asymptomatic.

There are well-defined biochemical abnormalities in the bile of patients with cholesterol stones. The liver secretes bile that is saturated with cholesterol and contains relatively less bile salts and phospholipids. These patients seem to have a complex derangement of lipid metabolism in the liver, for not only do they have a reduction in size of bile acid pool, but studies on North American Indian families with cholesterol gallstones suggest that there is also an increased rate of secretion of biliary cholesterol.

On the other hand, patients with pigment stones do not have any abnormality of biliary lipids. The association between pigment stones and haemolysis is well recognized though the reason for the precipitation of bile pigment remains obscure. The prevalence of gallstones is increased in cirrhosis of the liver. There is a disturbance of bile acid metabolism in cirrhotic patients. But the fact that the gallstones tend to be mainly of the pigment variety suggests that the most important factor in the pathogenesis of these stones may well be the haemolytic tendency which accompanies the cirrhotic process. There has been a change in the composition of gallstones in Japan over the last 40 years. During the 1920s the stones were mainly calcium bilirubinate and could be referred to a high prevalence of infections of the biliary tract. Since 1960 the gallstones appear to be predominantly cholesterol. The factors responsible for the change remain to be identified, but the significant one may be the change in food habits which has occurred in Japan since the second world war.

It would be of great interest to understand the events responsible for the presence of calcium palmitate in gallstones. The major biliary phospholipid is lecithin, which can be hydrolysed to lysolecithin and fatty acids by the enzyme phospholipase A. This is found in a variety of tissues and secretions, including snake venom and human pancreatic juice. Could it be that the contamination of bile by pancreatic secretions produces free palmitic acid, which then precipitates as calcium palmitate? The saturated fatty acid, palmitic acid, is attached to the C-1 ester position in the lecithin molecule, whereas phospholipase A releases the fatty acid from the C-2 position, and this is usually the unsaturated fatty acid oleic acid. Nonetheless R. Blomstrand and P. Ekdahl detected free palmitic acid when human biliary lecithin was hydrolysed by snake venom phospholipase A. It would be interesting to know whether calcium olate crystals occur in gallstones and, if not, why not.

The primary bile acid, chenodeoxycholic acid has been known to alter bile chemistry, thereby promoting the dissolution of gallstones. There is at present every reason to hope that this substance or some other detergent agent will provide a safe medical treatment for gallstones. One of the questions which will have to be answered is whether it will be possible to predict those stones likely to respond to the detergent therapy. Radio-opaque, calcium-containing stones may be less responsive to treatment with chenodeoxycholic acid, for G. D. Bell and colleagues have shown that stones which contain an outer rim of calcium are less likely than others to be influenced by a favourable ratio of bile acid plus phospholipid to cholesterol. At present the only way of assessing gallstone composition in vivo is x-ray examination. What is required is a mechanism for predicting gallstone composition more accurately than present radiological methods.

The best source of information would seem to be the biliary tract, and work is needed to relate in a detailed way bile chemistry to variation in gallstone composition.

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1 Nakayama, F., Journal of Laboratory and Clinical Medicine, 1968, 72, 602.
3 Sutor, D. J., and Wooley, S. E., Gut, 1971, 12, 55.
7 Buchanan, I. A. D., Clinics in Gastroenterology, 1973, 2, 49.
11 Buchanan, I. A. D., Gut, 1969, 10, 705.

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**Fetal Implants in Uterus**

On rare occasions tissues foreign to the uterus are found lying in the endometrium or endocervix. These reported are most often bone, cartilage, and neuroglia. The origin of this heterotopic tissue has aroused much debate. One theory incriminates chronic inflammation with necrosis of the wall of the uterus; this is followed by dystrophic calcification, which later undergoes osseous metaplasia. In this way the presence of heterotopic bone is explained. In one case of extensive endometrial ossification there was a long history of a high intake of calcium and vitamin D. The heterotopic cartilage could be explained in the same way as chondral metaplasia of chronic inflammatory granulation tissue. An alternative pathogenesis is that these tissues are elements of a mixed type of tumour—for instance, a teratoma. The mesodermal mixed tumour of the uterus also contains a variety of elements, which are histologically malignant.

C. W. Newton and M. R. Abell have recently described five further cases of heterotopic tissues in the endometrium and endocervix. Neuroglia was found in one case, cartilage in three others, and both cartilage and bone in the fifth. The patient's ages varied from 23 to 39 years, and they all had a prior history of instrumental abortion. This was usually followed by persistent, heavy, irregular menses with pain and the passage of blood clots, which lasted from 3 to 24 months before a diagnostic curettage or an abdominal hysterectomy was performed. In one case there was a polypoid mass at the external os. In all the cases the endometrium or endocervix was histologically normal apart from the heterotopic