about 35 mg. per 100 ml. While measurements of total salicylate are of some help in planning dosage and type of treatment, they do not give a reliable estimate of the amount of drug presented to the tissues, because a large but variable proportion is bound to plasma-protein—chiefly albumin.

To relate the known effects of salicylates upon the enzyme systems of intermediary metabolism to their anti-rheumatic properties is difficult. Salicylates have been shown to uncouple oxidative phosphorylation, to inhibit glutamic-pyruvic transaminase and malic dehydrogenase, and to suppress the biosynthesis of mucopolysaccharides in cartilage. Shift of fluid from inflammatory joint effusions might, for example, be due to uncoupling; but stronger uncouplers than salicylates have no such effect on effusions. As was well remarked at the symposium, before a biochemical metabolic effect can be related to therapeutic action, the dosage in each instance should be known to be comparable, and the same metabolic effect should be produced by other drugs with a similar therapeutic action; conversely, other substances producing the same metabolic effects should lead to the same therapeutic result. Other metabolic properties of salicylates discussed at the symposium included the lowering of serum-cholesterol in conditions of hypercholesterolæmia; the reduction of blood-sugar in diabetes; the impairment of urate clearance by small doses (larger doses, on the other hand, have a uricosuric effect); and the increase of total body water which, together with an increase in cardiac output and work, may occasionally induce heart-failure in patients with rheumatic fever and carditis. Salicylates also interfere with the binding of thyroxine by plasma-proteins and increase its rate of excretion; the uptake of ^{131}I-labelled triiodothyronine by red blood-cells in vitro is also accelerated. Salicylates have been shown to suppress a number of experimental immunological processes. In the guineapig they antagonise the bronchoconstrictor action of bradykinin (but none of its other effects) and delay the appearance of erythema induced by ultraviolet light. The anti-inflammatory action of salicylates may have two components—specific interference with enzyme systems, and nonspecific reduction of vascular reactivity.

The production of occult gastrointestinal bleeding by aspirin has now been confirmed repeatedly. The bleeding appears to result from the drug's local action on the gastric mucosa, for congestive and hæmorrhagic changes can be seen with the gastroscope. Long-term studies have shown that the degree of susceptibility is relatively constant in any one individual. Although the amount of blood lost is usually small, consumption of aspirin over long periods has led to iron-deficiency anæmia. Most physicians, however, who prescribe long-term aspirin treatment, believe that this risk is not sufficiently serious to outweigh the efficacy of the drug in conditions such as rheumatoid arthritis. The relation of aspirin to acute gastrointestinal hæmorrhage is less certain, but retrospective studies suggest that it may occasionally precipitate hæmatemesis.

In 1961, two hundred people died from salicylate poisoning in England and Wales. About four-fifths were adults, most of whom took the drug with suicidal intent; the remainder were children, and overdosage was accidental. The effects of salicylate intoxication on acid-base equilibrium are complex: there is an increase in fixed acid with a fall in plasma-bicarbonate, and increased alveolar ventilation with a fall in pCO_2—though this last effect is antagonised to some extent by the increased production of CO_2 following the uncoupling of oxidative phosphorylation. The final reaction of the blood depends on the relative influences of these different factors and may be acid, normal, or alkaline. The metabolic (as opposed to the respiratory) component is greater in children who excrete salicylate more slowly; acidosis is almost universal in infants under two, but follows only massive intoxication in older children and is very rare in adults. The intricacy of the situation makes biochemical control of the treatment of salicylate intoxication imperative; moreover, the data so provided must be correctly interpreted and a low total plasma-CO_2 must not be taken as necessarily indicating acidosis. Conservative therapy—the correction of deficiency of fluid, calories, and potassium—is usually adequate. But in severe cases the removal of salicylate by either alkalinising the urine or by hæmodialysis must be considered. The selection of patients for these procedures is difficult; but severely intoxicated patients should always be admitted to a hospital in the vicinity of an artificial-kidney unit so that, if hæmodialysis becomes necessary, it need not be unduly delayed.

POLYVINYL SPONGE IMPLANTS AND MALIGNANCY

BECAUSE polyvinyl sponge gives rise to little inflammatory or foreign-body reaction, it is used by plastic surgeons for cosmetic operations on the breast and elsewhere, and by some cardiac surgeons for patch-repair of septal defects. The material has hitherto been regarded as harmless; but now some reservation seems necessary.

Horning showed [1] that there was some correlation between carcinogenicity and the surface area of implanted polyvinyl films. Soon after planning new experiments to compare the long-term effect of "thin" sponges and "thick" sponges, Professor Horning died. Dukes and Mitchley [2] have continued the work. They found a malignant tumour—a spindle-cell sarcoma—in only 1 out of 20 rats after the implantation of "thin" sponge. But when "thick" sponge of cross-linked polyvinyl alcohol ('Ivalon'), 2 cm. × 5 mm., was implanted subcutaneously, it was followed by sarcoma in 14 out of 20 rats which survived long enough for a palpable tumour to appear. In each of these, dissection and microscopic examination showed that the malignant tumour had arisen from tissues adjacent to the sponge. Dukes and Mitchley conclude that polyvinyl sponge may eventually be carcinogenic for rats if left long enough in the tissues, and that carcinogenicity is related to the size and thickness of the implanted sponge. They cite various workers [3–6] who were unable to find any record in man of cancer arising near plastic implants. But, in 8 implants removed from patients four to eighteen months after they had been introduced, Dukes and Mitchley found that the initial tissue response resembled that in the rat.

Is the long-term effect the same in man as in the rat? This question cannot yet be answered. Meanwhile, Dukes and Mitchley advise surgeons to use sheets of sponge as thin and porous as possible, and, where they can, to remove the sheets when they have served their purpose.

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