after α-methyldopa (100 mg/kg). Mean decrease 3 hr after α-methyldopa alone was 35 mm Hg (S.E. of mean=6.5, n=13) and after α-methyldopa plus MK-485 39 mm Hg (S.E. of mean=8.0, n=8). The difference was not statistically significant. MK-485 alone lowered blood pressure slightly after 12–24 hr. The accumulation of α-methyldopamine was inhibited to 100% in heart and in femoral muscle but was unchanged in brain by pretreatment with MK-485.

Thus, inhibition of the synthesis from α-methyldopa of false transmitters in peripheral sympathetic nerves does not influence the hypotensive response of the drug, but this effect is abolished when the inhibition is extended to the central nervous system.

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Vasodilatation and oxygen uptake in skeletal muscle of the dog

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It is considered that oxygen uptake of a resting muscle can be increased by augmenting the blood flow and the number of open capillaries in the muscle. The oxygen uptake of the isolated gastrocnemius or gracilis muscle in dog was determined following vasodilatation caused by either nervous or humoral mechanisms, in order to study their point of action. The venous blood from the muscle was directed through a cuvette where oxygen saturation was continuously estimated by reflexion oximetry. The arterial oxygen saturation was also determined. Blood flow was measured by a silicone filled drop counter on either the arterial or the venous side.

Activation of the sympathetic cholinergic vasodilator nerves caused a vasodilatation lasting about 2 min. This vasodilatation led to an initial increase in oxygen uptake followed by a return to resting values even though the blood flow remained at the augmented level. This is somewhat at variance with the results of Rosell & Uvnas (1962), who, in skeletal muscle of cat, found a decrease in oxygen uptake after an initial increase following sympathetic cholinergic vasodilatation.

Acetylcholine, infused I.A. at 0.1–0.5 μg/min per 100 g muscle caused a dilatation. During the first 10–30 sec of this vasodilatation the oxygen uptake increased but then returned to resting values and remained there even when the vasodilatation was prolonged over 4–5 min.

Vasodilatation was further caused by inhibition of vasoconstrictor nervous tone. The carotid sinus nerve was stimulated and, to avoid the effect of the blood pressure fall, the muscle to be studied was cross-perfused from a donor dog. In this case oxygen uptake was increased during the whole period of stimulation, provided the blood flow was kept increased.

Some conclusions concerning the sites of action of vasodilatory mechanisms can be drawn from these experiments. The sympathetic cholinergic vasodilator nerves and acetylcholine seem to dilate preferentially at the arteriolar level. The increased blood flow caused by these mechanisms initially passes nutritional channels leading to increased uptake of oxygen, but are later directed through more non-nutritional pathways, a sort

of physiological shunt mechanism. On the other hand, the increased blood flow caused by inhibition of vasoconstrictor nervous tone seems to be directed through nutritional capillaries during the whole period of vasodilatation. This dilatation should therefore take place, both in the arterioles, and also more peripherally, in the precapillary sphincter region.

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Kallidin—a probable factor in the pathogenesis of malaria

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Tella & Maegraith (1966) suggested that bradykinin was involved in the pathological manifestations of malaria. It became of interest to see whether kallidin was also involved. Kallidin was prepared by incubating acid-treated plasma with urinary kallikrein. Plasma kallidinogen contents were then estimated by assaying the kallidin so produced against synthetic bradykinin.

Acid-treated plasma (Horton, 1958) was obtained from the blood of healthy rhesus monkeys (*Macaca mulatta*) and from those infected with *P. knowlesi* malaria (Tella & Maegraith, 1965). Kallikrein was prepared from pooled urine samples collected from fifteen healthy rhesus monkeys using a modification (Guth, 1959) of the method of Gaddum & Horton (1959). This monkey urinary kallikrein preparation gave a yield of 0.3 mg/ml. urine and an activity of 0.4 unit/mg when assayed against Glumorin. Recoveries of 80–90% were obtained by this method.

Maximum yield of kallidin was acquired by incubating 0.4 unit monkey urinary kallikrein with 5.0 ml. of acid-treated plasma at 37° C for 90 min. The yield from healthy monkeys was 8.9–10.3 mg/ml. plasma, and, when assayed on the isolated guinea-pig ileum, the biological activity was equivalent to 0.6–0.7 μg of synthetic bradykinin. The corresponding figures for the infected monkeys were 4.2–10.3 mg and 0.1–0.7 μg respectively, depending on the severity of the infection at the time blood samples were collected for kallidin estimation. Recoveries by this method were 70–80%.

The results showed that whereas the plasma levels of kallidinogen in healthy rhesus monkeys was approximately constant, in the infected animal they dropped sharply from the third day as the infection became intensified. There is thus a suggestion of an increase in the plasma level of circulating kallidin during the infection.

The behaviour of kallidinogen in these studies runs parallel with that of bradykininogen (Tella & Maegraith, 1966). Consequently, the same interpretations would apply.

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