between the beats. During vagus standstill or slowing and weakening a rhythmical series of artificial excitations calls forth beats showing a progressive increase in size (staircase); this indicates an influence inimical to the force-depressing power of the vagus on the ventricular muscle. The actual effect of the vagus on contraction force depends on an interaction between the influences of rate changes and the direct force-depressing power of the nerve. In opposition to the current view that the vagus has no direct effect on the contraction force of the mammalian ventricles the present investigation affords abundant evidence of strong weakening effects, in exceptional instances more extensive than those seen in the auricles. The weakening action of the vagus on the ventricles differs in certain important respects from what holds good in the auricles, being differently conditioned by rates of beat, etc. In the auricles vagus weakening may occur without any change of rate, and acceleration (by artificial excitations) of slowed and weakened auricles does not produce the augmenting effects seen in the ventricles.

The Cardiac Sympathetic.

As regards sympathetic action it is clear that the acceleration induced may, in Type II, determine marked augmentation in the ventricles. But it is plain that such is not the sole mode of action of the nerve, for the augmentation may be much greater than results from simply bringing the heart rate to the optimum frequency level. And large augmentation may be obtained by sympathetic stimulation while Type I is present in both ventricles and auricles. Hence rate change is only a possible contributory factor in the ventricles in Type II. There is a further specific influence beyond the direct effects of rate changes, in the case of stimulation or section of either the cardiac augmentor or the inhibitory nerves, and operative on both the auricular and the ventricular contraction force.

THE MECHANISM OF VOLUNTARY MUSCULAR FATIGUE.*

BY

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THE present inquiry deals with two forms of fatigue in man: (1) that induced by a series of voluntary contractions of the flexor digitorum sublimis, recorded by a Mosso's ergograph; (2) static contraction of the same muscle maintaining weights at certain levels and registered in the same way. Animal experiments (under anaesthesia) were also performed, the tibialis anticus of the rabbit and cat being used; contraction against an elastic resistance was registered graphically under different conditions. The relations of experimental ischaemia to the incidence and characters of fatigue were examined both in the human subject and in animals.

Fatigue from Serial Voluntary Contractions.

When fatigue results from a series of voluntary contractions the failure of effective muscular response is primarily "central"—that is, it is primarily due to defective outgoing motor impulses from the central nervous system. This is shown by the fact that further muscular response can still be obtained from electrical stimulation of the median nerve or of the muscle directly by single induction shocks or by faradic currents at rates of 40 to 200 per second. But though the fatigue is primarily central it is not always wholly so; there is evidence of marked depression of contractility in the muscle itself, at least when fatigue is induced by a very rapid series (for example, 120 to 160 per minute) of voluntary contractions, especially when the weight raised is considerable—for example,

2 kilos. Here there is an overlapping of central and peripheral changes. On the other hand, when a slow series (40 to 80 per minute) of voluntary contractions is employed to produce fatigue the muscular response to direct electrical stimulation may be practically unimpaired at the point of time when voluntary effort fails to raise the weight; the failure is distinctively central in this case.

The comparative effects of electrical excitation of the nerve trunk and of the muscle directly do not afford evidence of any marked selective influence of fatigue on the field of conjunction of nerve and muscle—the myoneural junction. The power of the contractile response obtained from (a) the nerve trunk, and (b) the muscle directly stimulated shows little difference even in advanced fatigue involving a great diminution of the available muscular energy. For example, in a rabbit's limb with intact circulation there was only a slightly greater response from (b) after about 50,000 contractions (pulling against an elastic resistance) had been executed in a period of four and a half hours, with reduction of the excursions to less than one-tenth of their original size. Such results are opposed to the hypothesis that comparatively early failure of transmission through the junctional region between nerve and muscle plays an important part in the genesis of voluntary fatigue.

Some previous observers have stated that after fatigue has been induced by direct electrical stimulation, voluntary effort can still cause effective contraction. In the present inquiry it has been found that after thorough fatigue has been induced by local stimulation voluntary impulses fail to elicit any marked further contraction.

Fatigue in the Ischaemic Condition.

In the ischaemic arm muscular fatigue from a series of voluntary contractions occurs much more rapidly than in the normal limb—for example, in two to three minutes, as compared with fifteen to twenty minutes. The direct depressant effects of the bloodless condition of the working muscle might be supposed to account for this, but it is found that local excitation (median nerve or body of muscle) still gives a marked, though reduced, contractile response. The fatigue is primarily in the central nervous system in this case also; weakening of the muscle develops as well, though much more slowly than the voluntary failure.

Why should central failure occur much more readily here than in the limb with normal circulation, since the central nervous system is far removed from the ischaemic area and beyond the reach of chemical agents, metabolites, etc., transmitted from the ischaemic limb? It is evidently contingent on afferent nervous impulses from the working muscle, depending on conditions set up in it by repeated strong contractions—conditions (chemical, etc.) naturally accentuated in the bloodless muscle setting up painful afferent impulses much more rapidly than in the normal arm.

Ischaemia *per se* cannot be regarded as the cause, for with quiescent muscle ischaemia up to a duration of fifteen minutes produces no discomfort and has no appreciable influence on the power of voluntary contraction. From the much earlier failure of response to voluntary effort during ischaemia it is evident that local conditions in the working muscle form part of the mechanism of fatigue. But the central nervous system is also involved, since further contractile response is given to local stimulation after voluntary effort has failed. The "central" failure is not simply a primary or direct one affecting some part of the central nervous mechanism concerned in voluntary motor discharge, but is largely a reflex effect of afferent impulses from the working muscle—no doubt protective against excessive prolongation of activity and undue development of fatigue in the muscle.

Thus the conditions of developing fatigue, arising primarily in the working muscle, do not directly induce the depression of contractile power shown in the ergographic records. Their influence is exercised in reflex fashion by afferent impulses concerned in producing the "central" failure which determines the ineffectiveness of voluntary effort (in both normal and ischaemic limbs).

at a point of time when there is still much contractile energy available in the muscle if effective motor impulses were provided. There is reason to regard the process of fatigue in the ischaemic limb as similar in most respects to what occurs with the intact circulation, though more rapid and acute.

Static Fatigue.

The onset of failure in this form of fatigue is of central origin, since when the continuous voluntary effort can no longer sustain the weight and prevent the shortening of the muscle from being overcome, the muscle can still respond strongly to direct electrical excitation. In this respect there is a general resemblance to the fatigue induced by a moderately slow (40 to 80 per minute) voluntary series of contractions. But in some other respects the two forms differ strikingly—for example, in relation to the influence of ischaemia.

The length of the period during which voluntary effort is effective in maintaining static contraction is very little affected by an ischaemic condition of the limb; indeed, the curves obtained in the normal and in the ischaemic states may be almost superimposable—in notable contrast to the rapid development of failure in voluntary serial contractions in ischaemia. Again, a period of static contraction has an improving effect (on contraction force), less than that of a period of rest, when interposed in the course of a series of voluntary contractions showing the progressive development of fatigue. There are indications which point to static fatigue with intact circulation as being essentially due to fatigue in the central nervous system, not dependent in any important degree on afferent impulses from the contracted muscle so far as evidence is available.

THE PINEAL GLAND.*

PROFESSOR HERRING (St. Andrews) showed a series of lantern slides illustrative of the histology of the pineal region of the mammalian brain. It was pointed out that the pineal body was not the remnant of the parietal eye found in some of the lower animals. The pineal body was a separate structure which was developed behind the parapineal organ or parietal eye. In man and most mammals the pineal body was bound up with the habenular and posterior commissures, but in the rat the pineal body lay on the surface of the brain between cerebrum and cerebellum. In this animal it was an isolated and highly vascular body which was suggestive of an organ of internal secretion. The pineal body of the cat was innervated only by fine nerve fibres, which entered it with the blood vessels. The mammalian pineal body contained a material which produced contraction of the melanophores of the tadpole, but its function was as yet unknown. Attention was drawn to the subcommissural organ of most mammals, which Dendy regarded as a receptor brought into action by changes in tension of the fibre of Reissner. The organ was well developed in most mammals, but was rudimentary in man.

PROTEIN METABOLISM IN CYSTINURIA.*

PROFESSOR D. MURRAY LYON and Mr. W. ROBSON, D.Sc. (Edinburgh), in a joint contribution, stated that various aspects of protein metabolism in a case of cystinuria had been studied. Cystine added to the diet to the extent of 20 grams over a period of four days was found to be quantitatively oxidized to inorganic sulphate. Likewise other amino acids were found to follow the normal paths of metabolism and to lead to increased urea excretion. Addition of sodium bicarbonate caused an increased output of cystine, practically the whole of it being in solution in the urine and only a small part in the urinary sediment. Disodium phosphate had no appreciable effect in producing the alkalinity necessary to hold in solution the cystine excreted. Changing the diet to one containing more protein gave rise to an increased excretion of cystine. The position of the "inborn error" was discussed.

* Brief abstracts of communications to the Section of Physiology and Biochemistry at the Annual Meeting of the British Medical Association, Edinburgh, 1927.

MODES IN WHICH DRUGS HAVE BEEN INTRODUCED TO USE.*

BY

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THE early history of the introduction of remedies is closely interwoven with the origins of primitive religions and, while reserving judgement on the theory that some animals have a crude idea of "first aid," it is highly probable that, since man's continuous effort has been to overcome the obstructions of Nature to his welfare and progress, his selfish instincts must have led him to seek means of defence against his personal injuries and diseases even before he evolved a communal religion.

The customs of primitive tribes show that the etiologies of diseases and misfortunes were first ascribed to malevolent human agencies, then to the interference of demons, and, progressively as religious beliefs developed, to infringement of a taboo, to neglect of ancestral spirits, and, finally, to an offended deity.

Among the least cultured peoples treatment commenced as a magical rite or exorcism, associated with the external application or internal administration of some medium; this medium or "drug" was essentially an amulet aiding the protection of the individual or the expulsion of the demon; in Polynesia, for example, the medicine given was "considered more as a medium by which the god would act than as possessing any power itself to arrest the disease."²

When these primitive rituals had as objective the benefit of the individual they became the basis of primitive therapy, but when they had as purport the protection of the community from pestilence, famine, or other calamity, they became the foundations of religious belief or of public hygiene in the tribe.

As diseases became differentiated so the number of etiological demons multiplied; thus, there were evolved specialist medicine men and an expanding list of exorcising remedies of specific purport; in other communities exorcism or propitiation of several demons or deities was attempted by repetition of the magical rite or by numerical grouping of the remedies or the times of their administration. A typical instance of this phase is recorded by Rivers at Eddystone Island, where epilepsy is treated by stroking the patient with four leaves and calling on "four ancient women" of the tribe, the treatment being performed on the last four days of the waning moon and repeated after four months.³ This case shows the primitive use of herbs purely as amulets, associated with the numerical arrangement of the rite and the herbs to influence four etiological factors, and indicates a primitive belief in the influence of the satellite on epilepsy.

Early Vedic literature provides confirmatory evidence of these views; thus, in the Atharva-Veda (circa 1000-700 B.C.), treatment is uniformly magical in type and curative agencies are amulets; the exorcisms may be directed against a human sorcerer or demons, or an offended deity is propitiated.⁴ The remedies were chosen on religious or mythical grounds; thus, butea and the soma plant were of great holiness; lead,⁴ catechu, colocynth, cannabis, and mustard had potent demon-dispelling powers; while curcuma was used for jaundice because of its yellow colour—a type of sympathetic magic.⁵ Liquorice was a charm to secure the love of women, and ricinus was a component of a battle charm.⁴ In Zoroastrianism also drugs were utilized chiefly as charms to expel demons.⁶

Although there is some evidence, both from the primitive tribes in the Philippines and in America and also from the classical period, that drugs were tested upon animals and sometimes upon man, the evidence from primitive medicine regarding the evolution of drugs is against experimental therapeutics and in favour of the opinion that they were originally used for driving out the demons of disease from the body; hence we find in primitive therapy a preponderance of remedial measures having effects as purgatives,

* Read in the Section of the History of Medicine at the Annual Meeting of the British Medical Association, Edinburgh, 1927.