Brit. J. Pharmacol. (1958), **13**, 138.

EFFECTS OF RATE OF STIMULATION AND OF FATIGUE ON THE RESPONSE TO NEUROMUSCULAR BLOCKING AGENTS

BY

L. WISLICKI

From the Department of Pharmacology, The Hebrew University-Hadassah Medical School, Jerusalem

(RECEIVED DECEMBER 11, 1957)

The response to neuromuscular blocking agents, as exemplified by suxamethonium and tubocurarine, may differ between symmetrical muscles. Increased rates of stimulation and fatigue both increase sensitivity to blocking agents. During recovery from suxamethonium block muscles may show a transitory failure to react to each stimulus with a contraction. Fatigue caused by prolonged indirect stimulation is prevented equally well by suxamethonium and tubocurarine in doses producing a complete block. The mechanism and significance of these findings are discussed.

Sensitivity to neuromuscular blocking agents varies between different muscles; for instance, the external muscles of the eye are paralysed by smaller doses than are necessary to paralyse the muscles of the limbs (Paton, 1953). These disparities may be related to the frequency of the impulses which the various muscles receive *in vivo* from the central nervous system. This rate is much higher in the external ocular muscles than in those of the extremities (Denny-Brown, 1929; Adrian and Bronk, 1929; Cooper and Eccles, 1930). Quantitative studies on the influence of rate of stimulation on neuromuscular block have been made in the rat phrenic nerve-diaphragm preparation (Chou, 1947), in dogs by means of electromyograms (Guyton and Reeder, 1949), in cats and dogs with regard to respiratory depression (Li, Jacobs, Aviado, and Schmidt, 1952), and in the rat sciatic nerve-gastrocnemius preparation (Preston and Maanen, 1953). All these investigations showed that increased frequency of stimulation resulted in a decrease in the amount of drug required to produce the same degree of block.

The response to blocking agents may also be altered by fatigue because during fatigue, as in partial block, the twitch tension of the muscle is diminished (Gilson, Schoepfle, and Walker, 1947; Brown and Burns, 1949). Symptoms resembling those that follow violent exercise may appear in man after an injection of suxamethonium though not after tubocurarine (Churchill-Davidson, 1954; Price, 1954).

The experiments described in this paper, some of which have been briefly reported (Wislicki, 1956), concern the influence exerted by variations in the rate of stimulation and by fatigue on the paralysis caused by suxamethonium and tubocurarine. The effect of prolonged block on the response of the muscle to a further dose of the same drug was also investigated.

METHODS

Anaesthesia in cats was induced with ether and maintained with intravenous pentobarbitone sodium. A carotid artery was cannulated for blood pressure measurements and a femoral vein for injections. Respiration was recorded by means of a tambour connected to a tracheal cannula whose side arm was fitted with an adjustable leak.

The tendon of each gastrocnemius was attached to an isometric lever. Both sciatic nerves were divided high in the thigh and the peripheral ends placed on shielded silver electrodes, the proximal electrode being the anode. Repetitive supramaximal rectangular stimuli of 0.1 msec. duration were applied from a Fleming stimulator. When both sides were stimulated simultaneously at the same frequency the two pairs of electrodes were connected to one channel. For the experiments where the rates of stimulation were different for each leg the two channels were separated by placing a Muirhead D-106-A/1 transformer between each channel and its electrodes, for which arrangement I am indebted to Mr. J. Weinman.

Suxamethonium chloride and tubocurarine chloride were the blocking agents used. Doses are given in terms of these salts. In those animals which received

several injections, only small doses were administered and intervals of at least 15 min. for suxamethonium and 50 min. for tubocurarine were allowed between injections to avoid accumulation, except in those experiments in which a prolonged complete block was required.

RESULTS

When stimulation was applied to both legs simultaneously at the same frequency, the response to blocking agents often differed between the two sides (Fig. 1).

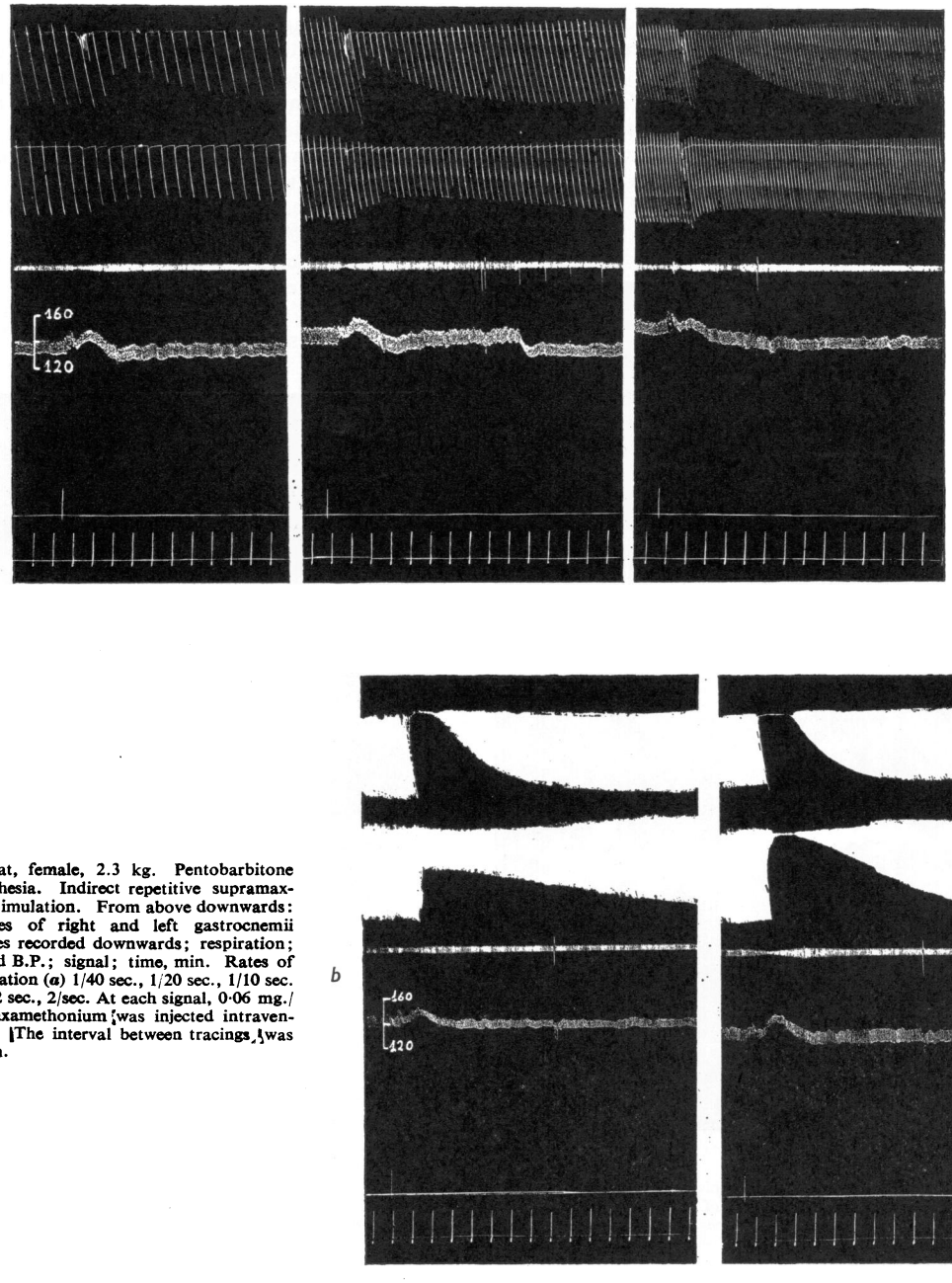

FIG. 1.—Cat, female, 2.3 kg. Pentobarbitone anaesthesia. Indirect repetitive supramaximal stimulation. From above downwards: twitches of right and left gastrocnemii muscles recorded downwards; respiration; carotid B.P.; signal; time, min. Rates of stimulation (*a*) 1/40 sec., 1/20 sec., 1/10 sec. (*b*) 1/2 sec., 2/sec. At each signal, 0·06 mg./kg. suxamethonium was injected intravenously. The interval between tracings was 15 min.

Disparities could be seen with any frequency of stimulation but were usually more striking at relatively high frequencies, such as 1/2 sec. in Fig. 1. The difference in sensitivity between the two sides, measured as the ratio of equi-active doses, might be as great as 1.5:1.

Fig. 1 also shows that the reaction to suxamethonium depended on the rate of stimulation. At 1/40 sec. 0.06 mg./kg. depressed contractions only slightly, but the effect of the same dose was much greater at higher frequencies. Transmission in the more sensitive gastrocnemius was completely blocked at 1/2 sec. and in the other muscle at 2/sec. To produce a block of a certain intensity during repetitive stimulation at 1/40 sec. about twice the dose of suxemethonium was required as at 1/sec. and 3 to 5 times the amount as during subtetanic stimulation. At rates of less than 1/30 sec. the effect of a dose of a blocking agent varied very little (25 animals).

The response to tubocurarine varied with the frequency of stimulation in the same manner (Fig. 2).

When during subtetanic stimulation a transient block was produced by a small dose of suxamethonium, the first contractions to appear during recovery often had a frequency lower than the rate of stimulation. The ratio between the two frequencies varied in different experiments. In the experiment illustrated in Fig. 3 a frequency of 15 shocks/sec. caused a subtetanus which was blocked by 0.06 mg./kg. suxamethonium. Within 2 min. contractions returned at a rate of 8/sec., gradually increasing in size for about half a min. The twitches then became more frequent but smaller, and subtetanus reappeared.

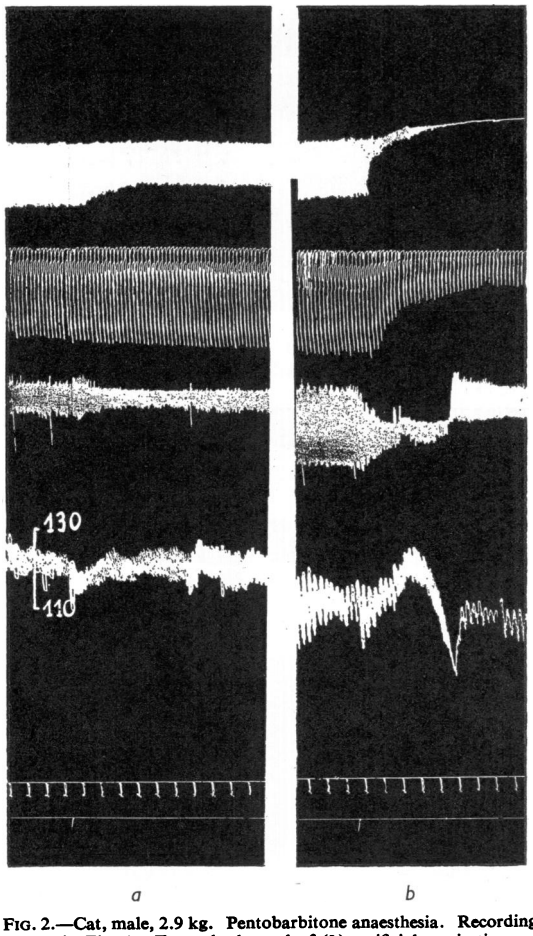

FIG. 2.—Cat, male, 2.9 kg. Pentobarbitone anaesthesia. Recordings as in Fig. 1. Towards the end of (*b*) artificial respiration was given. Rates of stimulation: upper muscle record, 1/sec.; lower muscle record, 1/10 sec. At the signals tubocurarine was given intravenously, at (*a*) 0.15 mg./kg., and at (*b*) 0.25 mg./kg. The interval between tracings was 50 min. Time, 1 min.

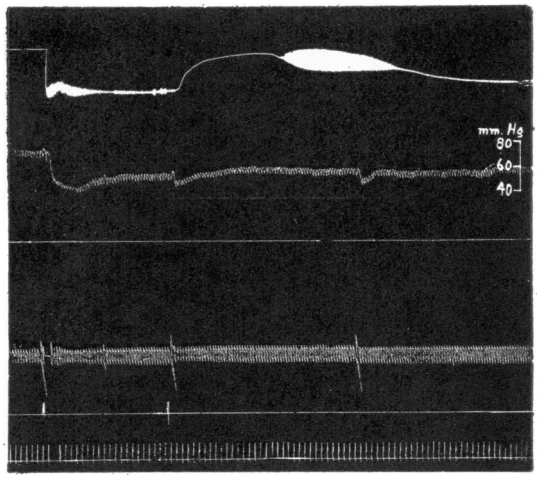

FIG. 3.—Cat, male, 3.2 kg. Pentobarbitone anaesthesia. Indirect supramaximal stimulation at 15/sec. From above downwards: gastrocnemius twitch; blood pressure; zero line for blood pressure; respiration; signal; time, 5 sec. At the first signal stimulation was started and at the second 0.06 mg./kg. suxamethonium was injected intravenously.

This transient discrepancy in frequencies of stimulation and response was not observed after large doses of suxamethonium given during subtetanic stimulation or with small amounts injected during tetanic contraction.

The influence of muscle fatigue on the effect of blocking agents was studied by testing the response of the same muscle after prolonged stimulation at high and low frequencies (Fig. 4). For 45 min. one gastrocnemius was stimulated at 1/10 sec., the other at 3/sec. Neither muscle showed signs of

fatigue, the twitch height remaining constant. Then 0.75 mg./kg. suxamethonium was injected while stimulation continued at the same frequencies. In the muscle stimulated at 1/10 sec. the response was very slight while in that stimulated at 3/sec. transmission ceased for 3 min. The channels of the stimulator were then switched so that the muscle which had been stimulated at 1/10 sec. was now stimulated at 3/sec. and *vice versa.* After a few minutes, the same dose of suxamethonium now caused complete block in both muscles (Fig. 4*a*).

exclude this possibility the new rates of stimulation were maintained for an hour and the same dose of suxamethonium was injected again. It now caused a complete block in the muscle stimulated rapidly and only a partial block in the muscle stimulated slowly (Fig. 4*b*). The stimulation was again reversed and, within a few minutes, a further dose of suxamethonium produced complete block of both muscles.

This result was confirmed in 8 similar experiments. The reaction of the muscle to the action of suxamethonium was always intensified after

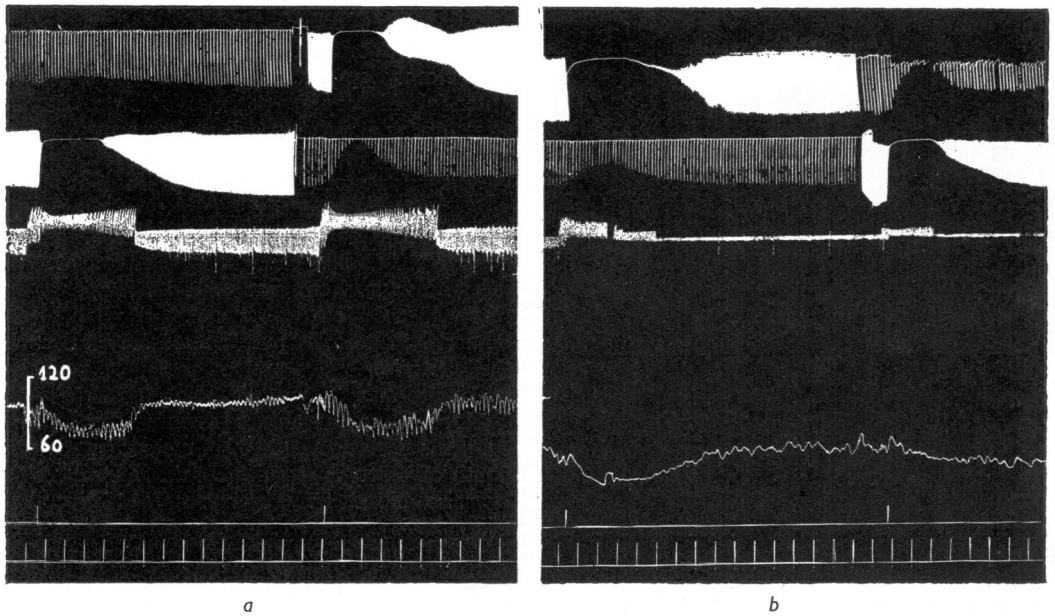

FIG. 4.—Cat, female, 3.5 kg. Recording arrangement as in Fig. 1. Periods of artificial respiration shown as elevations on respiratory tracings. At signals, 0.75 mg./kg. of suxamethonium was injected intravenously. Time, 1 min. See also table below this legend.

Muscle Recording	Rates of Stimulation			
	During 45 min. Prior to (*a*)	(*a*)	During Interval of 55 min. between (*a*) and (*b*)	(*b*)
Upper ..	1/10 sec.	1/10 sec., later 3/sec.	3/sec.	3/sec., later 1/10 sec.
Lower ..	3/sec.	3/sec., later 1/10 sec.	1/10 sec.	1/10 sec., later 3/sec.

This increased response during stimulation at low frequency in the muscle previously subjected to high frequency stimulation for 45 min. might conceivably have been due to an initial difference in sensitivity between the two gastrocnemii. To

prolonged rapid stimulation. This effect was reversible provided that the twitch tension remained unchanged throughout, indicating that only a slight degree of fatigue was present.

The effect of a blocking agent on a severely fatigued preparation is recorded in Fig. 5. The gastrocnemius of one leg was allowed to rest while the other was stimulated at 4/sec. for 2 hr., thereby reducing the twitches to a fraction of their initial height. Both muscles were then stimulated at 1/10 sec. for 5 min., and 0.05 mg./kg. tubocurarine was injected. This had hardly any effect on the rested muscle, but in the fatigued one a complete block developed. Moreover, the preparation did not recover completely since the twitch tension remained smaller than it had been before the injection of tubocurarine.

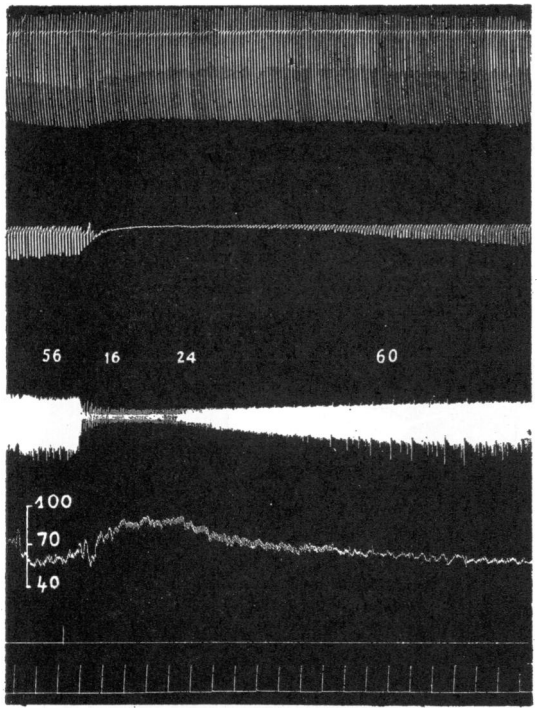

FIG. 5.—Cat, female, 3.5 kg. Recording arrangement as in Fig. 1. The muscle recorded at the top was after rest, but the lower muscle recording was after stimulation at 4/sec. for 120 min. The numerals above the respiratory tracing signify respiration rate. At the signal 0.05 mg./kg. tubocurarine was injected intravenously. Time, 1 min.

It seemed possible that the block produced by suxamethonium might be accompanied by changes of the neuromuscular junction comparable to those occurring during fatigue. This was tested in the following way. A gastrocnemius was stimulated at 2/sec. and its response to the test dose of either suxamethonium or tubocurarine was ascertained.

The frequency was then increased to 4/sec., and, with stimulation continuing all the time, the same blocking agent was administered in very large amounts: 1 mg./kg. suxamethonium or 0.4 mg./kg. tubocurarine was given repeatedly as required to maintain a complete block for 2 hr. Stimulation was then switched back to 2/sec., and when the preparation had recovered from the block the same test dose as at the beginning was administered again. With both suxamethonium and tubocurarine the reaction to this last injection was found to be the same as to the initial dose, indicating that the muscle had not been affected by the fast stimulation during the long period when transmission was blocked. Hence, no evidence was found for the assumption that the block produced by suxamethonium is accompanied by changes at the neuromuscular junction similar to those produced by fatigue.

DISCUSSION

The alterations in the effects of suxamethonium and tubocurarine with variations in the frequency of stimulation appear to be due to an effect of repetitive stimulation on the events which take place at the neuromuscular junction. Although the local and propagated potential changes last for only a few msec. they may be influenced by events which occur at much slower rhythms. Eccles, Katz, and Kuffler (1941) reported that after two closely spaced nerve volleys the end-plate potential did not recover for several seconds. Likewise, in the lightly curarized preparation, a brief tetanus is followed by electrical changes which may last for more than 98 sec. (Liley and North, 1953). Thus repetitive stimulation at intervals from 40 to less than 0.5 sec., as applied in our experiments, could have an increasing effect at the neuromuscular junction and thereby vary the response to blocking agents. By analogy, the higher the rate of impulses a muscle receives from the central nervous system the more sensitive it will be to such drugs.

Blood flow is another factor which, *in vivo*, determines the speed of development and the depth of a neuromuscular block. During rhythmic exercise blood flow is increased (Barcroft and Swan, 1953). Accordingly, the higher the rate of stimulation the greater will be the increase in blood flow and the widening of the vascular bed through the opening-up of more capillaries. Therefore, after intravenous injection of a blocking agent, its peak concentration in the tissues will occur earlier and will be spread over a greater number of neuromuscular junctions, the faster the rate of stimulation. Block will thus develop more quickly and to a greater degree. Variations of blood flow, although contributive, cannot, however, be decisive for the increase in the sensitivity to blocking agents observed with faster stimulation, since the same dependence has been found *in vitro* in the rat phrenic nerve-diaphragm preparation (Chou, 1947) where differences in blood flow do not apply.

Muscles under subtetanic stimulation, when recovering from block due to a small dose of suxamethonium, showed a transitory failure to contract after each impulse. Brown and Burns (1949) demonstrated, in the fatigued muscle, the presence of a neuromuscular block. They found

that muscle fibres to which transmission was failing responded to some, but not to all, nerve impulses. Here there is an apparent similarity between the effect of neuromuscular blocking agents and fatigue.

On the other hand, the effect of blocking drugs is intensified after exercise. This intensification precedes any diminution in twitch tension, for it occurs at a time when fatigue of the neuromuscular junction only can be involved. In fatigue, the decrease of twitch tension is not due to a depression of neuromuscular transmission but to a decline in contraction strength as the biochemistry of the contractile process becomes defective (Merton, 1954; Edwards and Lippold, 1956). This mechanism clearly differs from that of blocking drugs which reduce the twitch tension during partial block by preventing some of the muscle fibres from responding to stimulation.

I am indebted to Messrs. Allen and Hanburys Ltd. for a supply of "scoline."

References

Adrian, E. D., and Bronk, D. W. (1929). *J. Physiol.*, **67**, 119.

Barcroft, H., and Swan, H. J. C. (1953). *Sympathetic Control of Human Blood Vessels.* p. 45. London: Arnold.

Brown, G. L., and Burns, B. D. (1949). *Proc. roy. Soc.*, **B, 136**, 183.

Chou, T. C. (1947). *Brit. J. Pharmacol.*, **2**, 1.

Churchill-Davidson, H. C. (1954). *Brit. med. J.*, **1**, 74.

Cooper, S., and Eccles, J. C. (1930). *J. Physiol.*, **69**, 377.

Denny-Brown, D. (1929). *Proc. roy. Soc.*, **B, 104**, 252.

Eccles, J. C., Katz, B., and Kuffler, S. W. (1941). *J. Neurophysiol.*, **4**, 362.

Edwards, R. G., and Lippold, O. C. J. (1956). *J. Physiol.*, **132**, 677.

Gilson, A. S., Jr., Schoepfle, G. M., and Walker, S. M. (1947). *Ann. N.Y. Acad. Sci.*, **47**, 697.

Guyton, A. C., and Reeder, R. C. (1949). *J. Pharmacol.*, **97**, 322.

Li, T. H., Jacobs, B. R., Aviado, D. M., Jr., and Schmidt, C. F. (1952). Ibid., **104**, 149.

Liley, A. W., and North, K. A. K. (1953). *J. Neurophysiol.*, **16**, 509.

Merton, P. A. (1954). *J. Physiol.*, **123**, 553.

Paton, W. D. M. (1953). *Anaesthesia*, **8**, 151.

Preston, J. B., and van Maanen, E. F. (1953). *J. Pharmacol.*, **107**, 165.

Price, J. M. (1954). *Brit. med. J.*, **1**, 273.

Wislicki, L. (1956). *Fed. Proc.*, **15**, 501.