ON THE MECHANISM OF ACTION OF HEXAMETHYLENE-1,6-BISCARBAMINOYL CHOLINE BROMIDE (IMBRETIL)

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Hexamethylene-1,6-biscarbaminoyl choline bromide (Imbretil) is one of a series of compounds first studied pharmacologically by Cheymol and co-workers,[1-3] and independently by Klupp and associates.[4,5] The substance possesses a powerful neuromuscular blocking action and is used extensively, particularly in Europe, as a muscle relaxant in surgical anesthesia.[6-12]

There is general agreement that Imbretil possesses a depolarizing action at the motor end-plates but opinions differ with regard to the type of block produced. Several authors have reported that in animals[13-15] and in man[9-12] the block is dual in nature and consequently is antagonized by neostigmine. Others[16-18] believe that the paralysis is a consequence of depolarization, although as with other depolarizing drugs, prolonged administration of Imbretil in man may lead to a change in the characteristics of the block.[17]

Species difference may account for some of the disagreement, for even succinylcholine and decamethonium cause dual block in the majority of animal species.[19] Among the common laboratory animals, only the cat resembles man in its response to neuromuscular blocking drugs. In the majority of muscles of both the cat and man the block produced by decamethonium and succinylcholine is a consequence of depolarization of the motor end plates.[19-23] The present experiments were therefore carried out mainly on the cat. The results show that in the tibialis anterior muscle of this species the block produced by Imbretil is a consequence of depolarization, no evidence of dual block being obtained. In addition they provide a possible explanation of the apparent neostigmine antagonism obtained by others.

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Methods

The experiments were carried out on 11 cats and 6 white leghorn hens anesthetized with chloralose (8 ml./kg. of a 1 per cent solution) injected intravenously into a subcutaneous vein of the fore-limb or a wing-vein respectively. Pentobarbitone sodium (6 mg./kg.) was usually mixed with the chloralose solution to prevent the initial excitement stage, which occurs with chloralose alone.

In both cats and hens, perspex shielded platinum electrodes were placed on the sciatic nerve of one hind-limb and the nerve was twice ligated and cut centrally to the electrodes. The leg was fixed rigidly in a horizontal position by means of steel drills through the ankle and knee. In cats, the tendons of insertion of the tibialis anterior and soleus muscles were separated from the bone and attached to flat steel-spring semi-isometric recording levers. Care was taken, particularly with the soleus, to separate the muscle as completely as possible from the more powerful muscles in its vicinity. In hens, the tendon of the lateral head of the gastrocnemius muscle was similarly attached to a recording lever. Twitches and tetani, which were recorded on a kymograph in most experiments, were excited by rectangular pulses of 50 μsec. duration and of at least twice the strength necessary to evoke a maximal twitch. In view of the effects of lowered muscle temperature on the responses to neuromuscular blocking agents,[23, 24] care was taken to maintain normal temperature throughout each experiment. This was continually checked by means of a copper-constantan thermocouple inserted into the belly of a neighboring muscle. The trachea

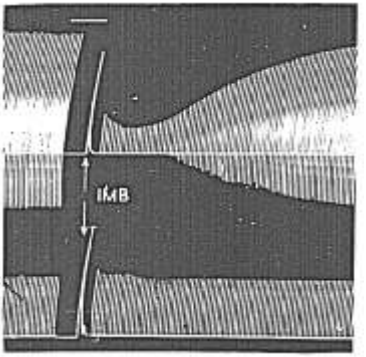

FIG. 1. Cat 3.2 kg. Maximal twitches of the tibialis anterior (upper record) and soleus muscles (lower record) elicited indirectly once every 10 seconds. At IMB, 5 μg. Imbretil injected intra-arterially. During the period marked by the horizontal bar, electrical stimulation was stopped.

was cannulated and respiration in cats was recorded by Gaddum's[25] method; artificial respiration was applied when necessary. In all experiments on cats, blood pressure was recorded from a common carotid artery. Since this was unaffected by the drugs used, these records are not included in the figures.

Action potentials were recorded from the cat's tibialis anterior by means of glass-mounted platinum electrodes inserted through the belly and the tendon of the muscle and from the hen's gastrocnemius muscle by means of concentric needle electrodes. After differential amplification by a Tektronix (type 122) battery driven pre-amplifier, the action potentials were displayed on a Tektronix (type 502) double beam oscilloscope. Electrical records of tension changes in the hen's gastrocnemius muscle were made simultaneously with the action potentials by means of an RCA 5734 mechano-electric transducer strain gauge. All electrical records were photographed on 35 mm. film.

Intravenous injections were made through a cannula in a jugular vein and washed into the circulation with 0.9 per cent w/v NaCl solution. Intravenous infusions were administered through a cannula in a femoral vein. Intra-arterial injections in cats were administered in a volume of 0.3 ml. through a needle-cannula inserted into the central end of the cut tibial artery below the tibialis anterior muscle. At the moment of injection the blood flow was arrested by briefly occluding the popliteal artery by means of a ligature placed around it just above the gastrocnemius muscle.

The drugs used were hexamethylene-1,6-biscarbaminoyl choline bromide (Imbretil),

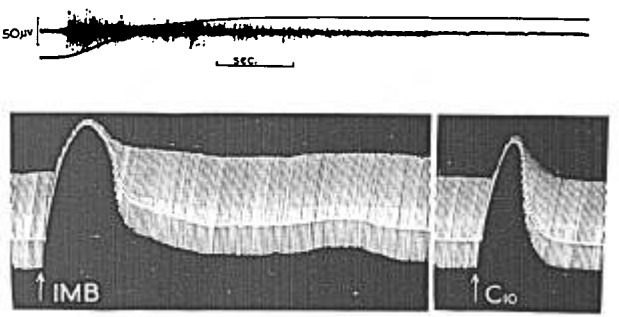

FIG. 2. Upper records: hen 2 kg. Tension and electrical changes produced in the gastrocnemius muscle by the intravenous injection of 2 μg./kg. Imbretil. Lower records: hen 2.3 kg. Maximal twitches of the gastrocnemius muscle elicited indirectly once every 10 sec. At IMB 2 μg./kg. Imbretil and at C_{10}, 5 μg./kg. decamethonium iodide injected intravenously.

decamethonium iodide, neostigmine methylsulphate and (+) tubocurarine chloride. The doses quoted in the text refer to the salts.

Results

Rapid intra-arterial injection of Imbretil in doses of 3 to 5 μg. caused a quick acetylcholine-like contraction of the tibialis anterior and soleus muscles of the cat. In comparison with the maximal twitch tension, the contraction produced by Imbretil in the soleus was always greater than that in the tibialis anterior muscle. With doses up to 8–10 μg. only the maximal twitches of the tibialis anterior muscle were subsequently reduced in tension although larger doses blocked both muscles. Figure 1 illustrates a typical result.

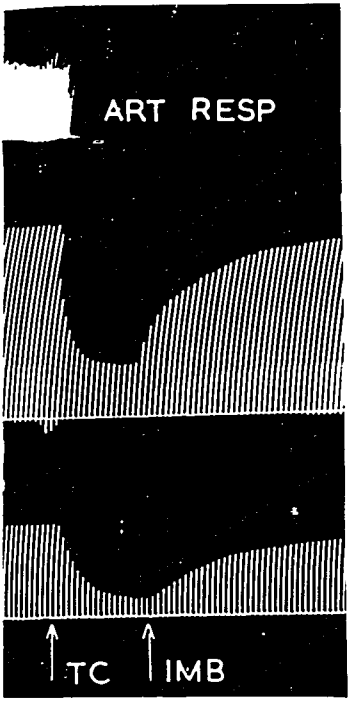

Fig. 3. Cat 2.9 kg. Upper record: respiration. Middle and lower records: maximal twitches of the tibialis anterior and soleus muscles respectively elicited indirectly once every 10 seconds. At TC, 0.4 mg./kg. tubocurarine and at IMB 10 μg./kg. Imbretil injected intravenously.

In hens, the intravenous administration of Imbretil in doses of 1 to 3 μg./kg. caused a contracture of the gastrocnemius muscle similar to that produced by other depolarizing drugs.[19, 26] Except with excessively large doses, the subsequent maximal twitches were not reduced in tension below the preinjection level. Figure 2 shows both an electrical and a kymographic recording of the contractural response to Imbretil in the gastrocnemius muscle of the hen. Imbretil was approximately five times more powerful than decamethonium iodide in this respect and the duration of its action was longer (fig. 2).

Like decamethonium and succinylcholine, a small dose of imbretil (10–20 μg.) injected at the height of a partial paralysis produced by tubocurarine in the tibialis anterior and soleus muscles of the cat, caused a rapid return of the twitch tension to normal (fig. 3).

In the cat, small doses of Imbretil (5–10 μg./kg.) injected intravenously caused fasciculations of the tibialis anterior and soleus muscles as well as of other muscles, the contractions of which were not recorded. The maximal twitches of the tibialis anterior muscle were markedly potentiated at this dose level and respiration was stimulated (fig. 4*a*). With slightly larger doses (10–20 μg/kg.) the fasciculations and the potentiation of the maximal twitches of the tibialis anterior muscle were followed by neuromuscular block. As with other depolarizing blocking drugs,[27] it was possible to cause complete block of the tibialis anterior muscle without abolishing spontaneous respiration or the maximal twitches of the soleus muscle. Figure 4*b* illustrates these effects. Still larger doses of Imbretil (25–40 μg./kg. and above) paralyzed the respiratory and soleus muscles as well as the tibialis anterior (fig. 4*c*). Imbretil was two to three times more potent than decamethonium iodide in its ability to

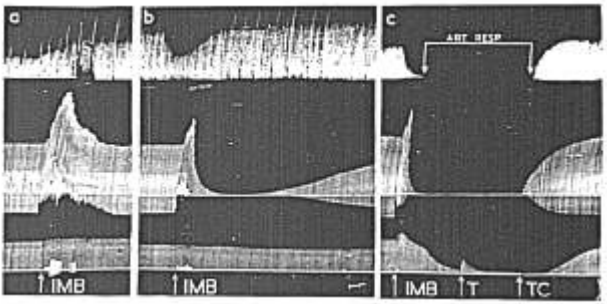

FIG. 4. *a* and *b*: Cat 3.3 kg.; *c*: Cat 3.1 kg. (*a* and *b* are from the same experiment). Upper record: respiration. Middle and lower records: Maximal twitches of the tibialis anterior and soleus muscles respectively elicited indirectly once every 10 seconds. At IMB, 10, 15 and 30 μg./kg. Imbretil respectively and at TC, 100 μg./kg. tubocurarine injected intravenously. At T, a motor nerve tetanus was applied for 5 seconds at a frequency of 50/second. The respiration record in *a* and *b* lags slightly behind the muscle records.

block the contractions of the tibialis anterior muscle.

During the paralysis of the tibialis anterior muscle, the tension of an indirectly elicited tetanus was well sustained and the subsequent twitches were neither increased nor decreased in tension. Neostigmine (50–100 μg./kg.), administered intravenously at the height of the paralysis, caused an increase in the depth of the block. Figure 5 illustrates these effects. In this experiment, spontaneous respiration continued after the injection of Imbretil but was abolished on the administration of neostigmine. After the injection of neostigmine the excess acetylcholine liberated during and following a tetanus is presumably able to persist long enough to summate with the blocking drug. Thus, after neostigmine, the

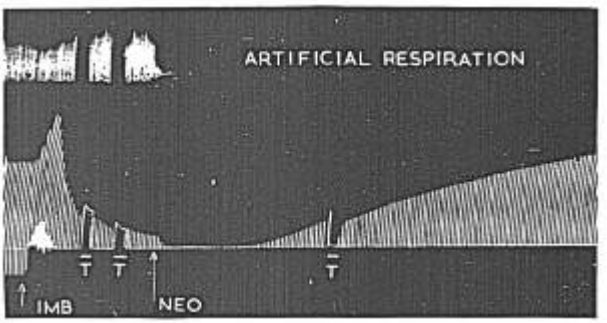

FIG. 5. Cat 3.8 kg. Upper record: respiration. Lower record: Maximal twitches of the tibialis anterior muscle elicited indirectly once every 10 seconds. At IMB, 15 μg./kg. Imbretil and at NEO, 50 μg./kg. neostigmine methylsulphate administered intravenously. At T, a motor nerve tetanus was applied for 5 seconds at a frequency of 50/second. During the tetani, the kymograph speed was increased.

tension of a tetanus was no longer sustained and the subsequent twitches were reduced in size (fig. 5). A small dose of tubocurarine (100 μg./kg.) administered intravenously at the height of the paralysis of the tibialis anterior muscle caused a rapid return of the twitch tension to normal. It also antagonized the respiratory paralysis produced by Imbretil. Figure 4c illustrates these effects of tubocurarine.

In the soleus muscle, on the other hand, tubocurarine caused a small increase in the depth of the block produced by Imbretil. In this muscle, tetanic tension during the block was not sustained and the post tetanic twitches were increased; the injection of neostigmine antagonized the paralysis. These indications that the block in the soleus muscle was dual in nature were evident with the first paralyzing dose of Imbretil, as illustrated in figure 4e, but they became more pronounced with subsequent injections. With repeated injections of Imbretil the block produced in the soleus muscle was reduced and it was necessary continually to increase the dose in order to produce the same degree of paralysis.

The block produced by Imbretil in the tibialis anterior muscle never showed evidence of a dual nature. Even in experiments in which the tibialis anterior muscle was repeatedly paralyzed with Imbretil and allowed to recover, the characteristics of the final block were the same as those of the first, being antagonized by tubocurarine, unaffected by tetanus and deepened by neostigmine. With the first two or three doses of Imbretil, each block was deeper than the preceding one but with subsequent injections some tachyphyllaxis was evident.

In order to determine whether prolonged administration of large amounts of Imbretil would produce a dual block in the tibialis anterior muscle, the drug was administered for up to 3 or 4 hours in the form of a continuous intravenous infusion, and the maximal twitch tension and the gross muscle action potential were recorded simultaneously. In these experiments it was found impossible to maintain a constant degree of partial paralysis without altering the rate of infusion and this was therefore adjusted throughout. After 40–60 minutes of continuous infusion the muscle usually became slightly less sensitive to the blocking action and the rate of injection was therefore correspondingly increased.

When the tension of the partially blocked twitches exceeded about 30 per cent of the normal maximal twitch tension, the muscle

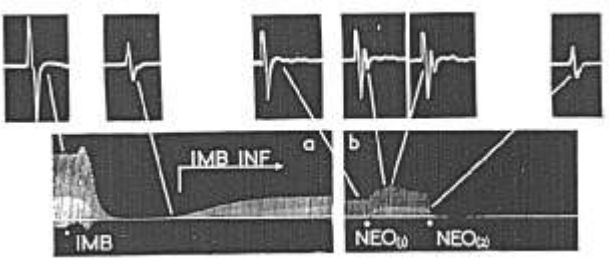

FIG. 6. Cat 3.4 kg. Upper records: gross muscle action potentials recorded from tibialis anterior. Lower record: Maximal twitches of the same tibialis anterior muscle elicited indirectly once every 10 seconds. The oblique white lines indicate the maximal twitches associated with the action potentials shown. At IMB, 10 μg./kg. Imbretil injected intravenously. The cat had previously received 2 similar injections of Imbretil. During the recovery period a continuous infusion of Imbretil was started and maintained throughout the rest of the experiment. Three hours and 10 minutes elapsed between *a* and *b*. At NEO (1), 30 μg./kg. and at NEO (2) 40 μg./kg. neostigmine methylsulfate injected intravenously. At the time of the first injection of neostigmine the animal had received a total of 0.323 mg. Imbretil in the form of a continuous infusion.

action potential, although reduced in voltage, showed evidence of repetitive firing. Small doses of tubocurarine (50 μg./kg.) abolished this repetition and at first caused a small decrease in twitch tension. The peak voltage of the action potential was not reduced, however, showing that the decrease in tension was not a consequence of fewer muscle fibers contributing to the gross tension. Subsequently, and particularly with slightly larger doses of tubocurarine (100 μg./kg.), the twitch tension and the peak voltage of the action potential rapidly increased. This effect was therefore due to an increase in the number of contracting muscle fibers.

Opposite results were obtained with neostigmine. Small doses (35 μg./kg.) caused a fairly pronounced increase in the tension of the partially blocked twitches and this was accompanied by a striking increase in the repetitive firing, although the peak voltage of the action potential was never increased. This is illustrated in figure 6. In this experiment, the peak voltage of the action potential was actually slightly decreased by neostigmine showing that, although the tension was increased, the number of muscle fibers contributing to it was reduced. A further injection of neostigmine at this stage usually had the opposite effect; the degree of block was enhanced, the action potentials were reduced in voltage and repetitive firing was abolished (fig. 6). Large doses of neostigmine always produced these latter effects immediately.

Discussion

The results confirm the findings by others that Imbretil possesses a powerful depolarizing action in both mammalian [9-18] and avian muscle.[12] Judging by the ability of intra-arterial injections of the drug to cause contraction of the nonstimulated muscle, the depolarization produced in the soleus is greater, with equal doses, than that produced in the tibialis anterior muscle. Despite this, the former muscle is more resistant to the blocking action. This difference in muscle sensitivity, which is also evident following intravenous injection, is similarly true for decamethonium and succinylcholine.[27-29] Burns and Paton [21] showed in the gracilis muscle of the cat that the block produced by depolarizing drugs, although a consequence of long lasting depolarization, is only indirectly so. The direct cause of the block is the electrical inexcitability to which depolarization gives rise at, and in the region immediately surrounding, the motor end-plates. Presumably, therefore, the muscle membranes are such that excessive depolarization leads to inexcitability more readily in the tibialis anterior than in the soleus muscle. That depolarization is not the direct cause of the block is also evident from the results of close-arterial injection into the tibialis anterior muscle. The over-all end-plate depolarization must be at its peak during the drug-induced contraction of the muscle but the subsequent block of the twitches does not reach its maximum until approximately one minute later.

In our experience, the initial fasciculations and potentiation of the maximal twitch produced by Imbretil in the cat were even more powerful than those produced by succinylcholine. Imbretil is known to possess some anticholinesterase activity [14, 15] and this may contribute to the effect since Zaimis [20] has shown that small doses of physostigmine and neostigmine markedly potentiate the fasciculations and twitch potentiation produced by decamethonium. Although Imbretil possesses anticholinesterase activity there was no evidence of muscarinic side effects, probably because the drug also possesses an atropine-like action.[14, 15] In any case, the anticholinesterase activity of Imbretil *in vivo* cannot be very marked for during the block of the tibialis anterior muscle, tetanic tension was well sustained and was without effect on the subsequent twitches. When cholinesterase is significantly inhibited, tetanic tension is not sustained and the subsequent twitches are depressed. Small doses of Imbretil readily antagonized the paralysis produced by tubocurarine but despite its anticholinesterase activity it was no more effective than decamethonium and succinylcholine in this respect. Kobinger and Kraupp [30] were unable to demonstrate any anti-curare action of polymethylene biscarbaminoylcholine compounds

in the isolated diaphragm preparation of the rat but decamethonium and succinylcholine are only weakly effective in this preparation, and the result obtained depends to a large extent on the composition of the bath fluid.

Throughout the paralysis produced by Imbretil in the tibialis anterior muscle the characteristics of depolarization block, such as is produced by decamethonium and succinylcholine, were exhibited. Even at a late stage in the block, or even after prolonged infusion, the paralysis was deepened by neostigmine and antagonized by tubocurarine. Block by these substances *in vivo* therefore differs from the "desensitization block" described by Thesleff[31] in the isolated tenuissimus muscle of the cat studied *in vitro;* under the conditions of his experiments, tubocurarine actually deepened the block produced by decamethonium and succinylcholine.

In experiments of the type described in this study, the sparing effect on respiration, in comparison with the effect of tubocurarine, is characteristic of depolarizing drugs.[32] This is probably only of experimental interest since, in conscious man, Unna and his coworkers[33, 34] showed that for a given degree of voluntary muscle paralysis, decamethonium was a more powerful respiratory depressant than the curare-like blocking agents. The explanation of this difference probably lies in the fact that spontaneous muscle movements do not resemble experimentally produced maximal twitches. Though not entirely similar, they do resemble experimental tetani and it is well known that tetanic tension during block by depolarization is well maintained. Thus, larger doses of depolarizing drugs are required to block spontaneous movements than to block the maximal twitches of the tibialis anterior muscle and respiration may, therefore, be little impaired during complete block of the twitch tension. Under tubocurarine, on the other hand, tetanic tension rapidly wanes and the dose to block spontaneous movements, including those of the respiratory muscles, does not differ much from that required to block maximal twitches.

Zaimis[19] first used the term "dual block" to describe the effects of decamethonium and succinylcholine on the muscles of many laboratory animals excluding the cat. Later, Jewell and Zaimis[29] showed that a similar dual block was produced by these substances in the soleus muscle of the cat. The present results show that Imbretil too, causes dual block in the soleus muscle of this species. Thus, although the drug produces initial fasciculation and potentiation of the maximal twitch, the block itself appears to be due to a raising of the threshold of the motor endplates to acetylcholine and is therefore antagonized by tetanus and by neostigmine and deepened by tubocurarine. Furthermore, the muscle shows the rapidly developing and marked tachyphyllaxis to the drug which is characteristic of dual block.

Several authors have described the effect of Imbretil in man as being dual in nature. Wiemers and Overbeck[12] describe it in this way despite the fact that they showed that small doses of methylcurarine abolished its effects and succinylcholine intensified its action at all times and in all doses. This description of the action of Imbretil is based almost entirely upon the fact that the various authors appeared to obtain some antagonism with neostigmine. However, it is perhaps significant that Wiemers and Overbeck found that the "antagonism" was slow in onset and appeared most reliably when neostigmine was injected in small doses at a late stage in the paralysis. These authors also point out that it was not always possible to differentiate between antagonism and spontaneous recovery. The present experiments provide a possible explanation of the apparent neostigmine antagonism obtained. When small doses of neostigmine were administered after 3 to 4 hours of continuous infusion of Imbretil, they often caused an increase in twitch tension. This effect could not be described as antagonism, however, since recording of the muscle action potential showed that it was merely due to the production of repetitive firing in some of the unblocked fibers rather than to an increase in the number of fibers contributing to the gross tension. In fact the number of fibers failing to contract was often slightly increased by neostigmine showing that the degree of block had actually

been increased although this effect was masked by the greater tension exerted by the unblocked fibers. Similar results are often obtained with single doses of depolarizing blocking drugs when small amounts of neostigmine are administered during the period of spontaneous recovery. At this stage, when the concentration of blocking drug in the region of the motor end-plates is rapidly diminishing, the amount of acetylcholine accumulating in the presence of neostigmine is presumably insufficient to summate with the blocking drug. It can, however, cause the unblocked fibers to fire repetitively and thereby exert a greater tension, as it does in a normal muscle, and this causes an apparently more rapid return of the twitch tension to normal. Blaber[25] recorded a similar effect during decamethonium paralysis with small doses of the powerful anticholinesterase, ambenonium.

The results obtained therefore fail to show any evidence of dual block produced by Imbretil in the tibialis anterior muscle of the cat and they therefore support the findings of Foldes *et al.*[17] and Christie *et al.*[18] with single doses of Imbretil administered to man. There is considerable evidence that after prolonged administration of large amounts of depolarizing drugs to man, the characteristics of the block undergo change. This has been called dual block but there is no convincing evidence that it is the same as that which always occurs in the muscles of most animal species and in the soleus muscle of the cat. One possibility which should not be overlooked is that after prolonged administration, the drugs may begin to reduce the output of transmitter from the motor nerve, possibly by an action similar to that of the hemicholiniums.[26] Such an action would account for the fact that neostigmine shows some weak antagonistic effect and that the muscles become sensitized to the action of subsequently administered tubocurarine.[27]

Judging from the results obtained in this study, Imbretil does not appear to possess any advantages over decamethonium as a muscle relaxant. The muscle fasciculations which precede the blocking action of succinylcholine are believed to be the cause of the postoperative muscle ache frequently experienced with this drug.[28] The muscle fasciculations produced by Imbretil in the present study were powerful and if this occurs to a similar extent in man it may constitute a disadvantage of the drug.

Summary

Hexamethylene-bis carbaminoylcholine bromide (Imbretil) has been shown to possess a powerful depolarizing action in the tibialis anterior and soleus muscles of anesthetized cats and in the gastrocnemius muscle of anesthetized hens. The block produced by Imbretil in the tibialis anterior muscle exhibited the characteristics of depolarization block, no evidence of dual block being obtained even when the drug was repeatedly administered either as single doses or in the form of a continuous infusion. In the soleus muscle, on the other hand, the block produced even by the first dose of Imbretil was dual in nature. When a partial paralysis of the maximal twitches of the tibialis anterior muscle was maintained for several hours by a continuous infusion of Imbretil, small doses of neostigmine often caused a striking increase in the tension of the partially blocked twitches. This effect was shown to be caused by repetitive firing of the unblocked muscle fibers. It was not a consequence of an increase in the number of fibers contributing to the gross tension and it could not, therefore, be described as antagonism.

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FAT EMBOLISM A combination of postprandial lipemia and ether anesthesia has been proposed as a cause of fat embolism. The mechanism postulated is that tiny droplets of fat in the blood are dissolved by the ether in the blood. As the blood passes through the pulmonary capillaries and the ether is excreted into the alveoli, the fat comes out of solution and is precipitated as free fat which becomes embolic. In the experiments here reported, attempts were made to produce fat embolism in this way. It did not occur. Postprandial lipemia is not a contraindication to the use of ether. (*Davies, J. I., and Peltier, L. F.: Deep Ether Anesthesia and Fat Embolism, A. M. A. Arch. Surg. 82: 417 (Mar.) 1961.*)

OBESITY A thousand patients were studied in order to determine what special hazards are associated with anesthetization in obesity. In the preoperative survey, hypertension, myocardial disease, and diabetes millitus were the most common pathological conditions. Furthermore, pulmonary function studies showed decreased tidal volumes and increased respiratory rates, and expiratory reserve volumes and vital capacity determinations which were at lower levels preoperatively in the obese than in the nonobese patient. In the operative period, "mechanical" hazards are associated with the manual dexterity and skill of the anesthesiologist in handling venipuncture, endotracheal intubation, and lumbar puncture. During inhalational anesthesia, respiration should be augmented or controlled. In the postoperative period, particular attention should again be given to respiratory function, and intermittent positive pressure breathing should be prescribed routinely in the recovery room for obese patients. Pulmonary function studies showed that almost all very obese patients exhibited a 50 per cent reduction in ventilatory volumes from the first to the sixth postoperative day. There was no obvious correlation between method of anesthesia and degree of postoperative ventilatory depression. (*Catenacci, A. J., and others: Anesthetic Hazards of Obesity, J. A. M. A. 175: 657 (Feb. 25) 1961.*)

RED CELL LOSS IN BURNS Destruction of erythrocytes following burn injury has been well documented. The red cells are hemolyzed and disappear from the circulation. Measurements made with venous blood are inaccurate because of "piling up" of red cells on the venous side of the circulation. In animals which showed a 7 per cent loss from arterial blood, the severity of the anemia was greater than indicated by venous blood analysis. (*Saltz, N. J., and others: Red Cell Destruction Following Experimental Thermal Burns, A. M. A. Arch. Surg. 82: 360 (Mar.) 1961.*)