trated in Fig. 1 from which the values of $7.55 \pm 0.68$ cc of digitalis tincture/kg of frog are obtained. The corresponding values by the more exact method of maximum likelihood were calculated to be $7.55 \pm 0.58$ and the equation of the best-fitting line with dosages (X) in logarithmic units, $Y = 5.289X + 0.356$. The line drawn in by eye coincides well with that calculated (the broken line of the figure).

It happens in this example that the graphically determined $ED_{50}$, obtained in less than 10 minutes, agrees exceedingly well with the maximum likelihood solution arrived at independently after the expenditure of considerably longer time, even with the aid of an automatic calculating machine. Differences between the two procedures will rarely be of practical significance. In this example the standard error is somewhat larger by the graphic procedure due principally to the fact that the line drawn by eye was slightly flatter than the best-fitting line found by the least-squares calculation. While a difference in the estimated standard error of this magnitude would scarcely modify the pharmacologic inferences, it nevertheless emphasizes the approximate nature of the graphic estimation and points up the fact that in crucial cases the standard maximum likelihood solution should be used.

*Summary.* A log-probit graph paper is described by which a simple graphic estimation of the $ED_{50}$ and its standard error may be quickly made.

## 14777 P

## Cumulative Effects of Repeated Head Trauma of Minimal Intensity.* Observations on Experimental Animals.

C. G. TEDESCHI.

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This investigation is concerned with the immediate and delayed effects of repeated, minimal, blunt impacts on the head.

Using as traumatizing agent an apparatus which permitted the strength of the blow to be measured exactly, a mass of 453.6 g dropping with a velocity at the point of impact of 330.9 cm/sec. was found to be just insufficient to produce loss of consciousness or any other immediate or delayed ill effects in a normal animal (subconcussive trauma). It was this blow of minimum intensity that was used in the investigation of cumulative effects of repeated trauma.

One hundred twenty rats of the same strain and of approximately the same weight were used in the experiment. Of these, 60 were given 15 blows in close succession, one minute apart; the other 60 were given the same amount of trauma (15 blows) at longer intervals, from 2 to 6 days apart, in a 50-day period. Half of each group were struck on the stationary head, and the other half were made to strike the rapidly accelerated head against a stationary object.

In all experiments precautions were taken that the head of the animal should be struck at the same region each time and that in each of the two mechanisms all animals should receive a trauma of the same momentum at all times.

*Observations.* Cumulative effects, as revealed by temporary loss of consciousness, at times by death or by persisting changes in behavior, were clearly shown in all groups of animals as a result of the repeated trauma. The frequency with which ill effects were displayed in the different classes at the end of the experimental period is shown in Table I.

In the great majority of cases there was a certain correspondence between the effects of the trauma during life and the extent of

* Read at the May meeting, 1944, of the Massachusetts Psychiatric Society.

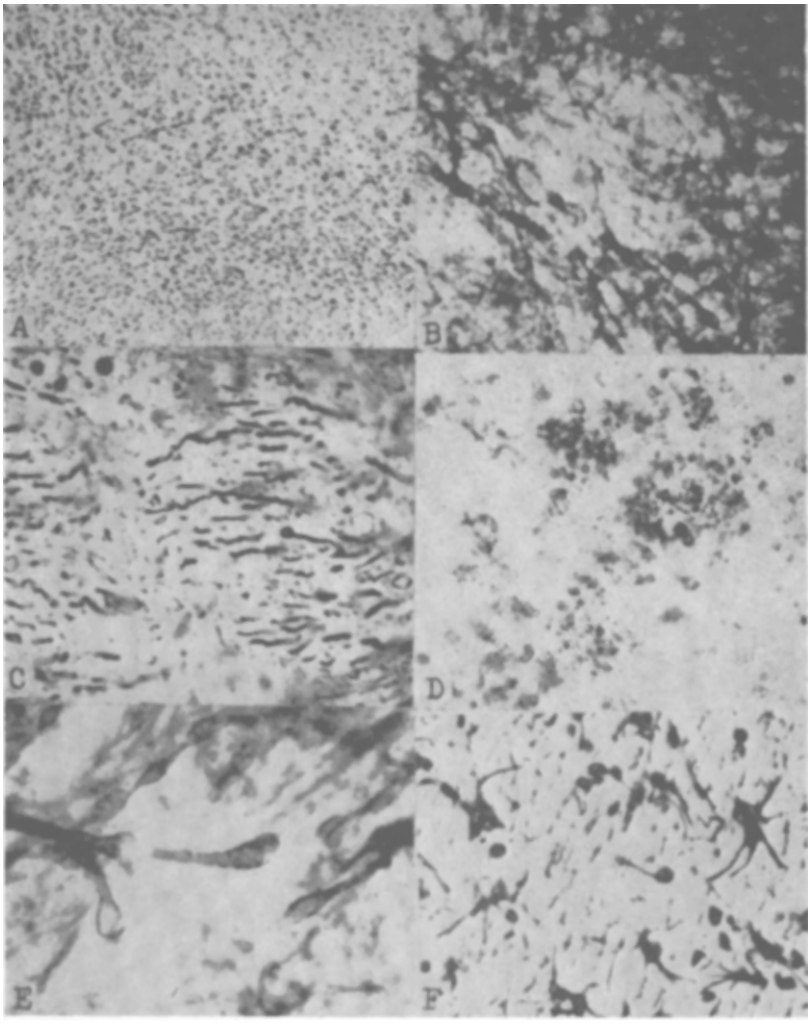


FIG. 1.

Microphotographs from the brain of a rat submitted to repeated subconcussive head trauma.

A. Obscuring of stratification, shrinkage and pyknosis of nerve cells in the cerebral cortex.

B. Disintegration with incipient reabsorption of myelin.

C. Breaking down of axons with bulbs of retraction at the ends of the fragmented fibers.

D. Scavenger cells, containing fat droplets, in an area of advanced demyelination.

E. Moniliform swelling of myelin sheaths, and club-like formations at the ends of degenerated portions of interrupted fibers.

F. Reaction of glial cells in an area with severe neuronal damage.

cerebral dramage, which appeared to be minimum in the animals clinically unaffected, and progressively more severe in the animals made unconscious, developing persisting changes in behavior, or dying as a result of the repeated trauma.

Hemorrhage or any other evidence of damage that could be detected with the naked eye was seen in only 7 out of 120 animals. Changes in neurons, affecting in a scattered fashion both nerve cells and nerve fibers, were, on the contrary, consistent microscopic

TABLE I.
Immediate and Late Effects of Repeated Subconcussive Trauma.

| Procedure | 15 blows | Unconscious (2″ to 60′) % | Persistent changes in behavior % | Death within 29 days % | No apparent effects % |
|---|---|---|---|---|---|
| Moving head against fixed object | 1 min apart | 73 | 13 | 17 | 27 |
| | 2-6 days apart | 57 | 7 | 17 | 43 |
| Moving object against fixed head | 1 min apart | 40 | 10 | 7 | 60 |
| | 2-6 days apart | 40 | 10 | 0 | 60 |

findings. Obscuring of stratification, shrinkage and pyknosis of nerve cells of the cortex, and demyelinated areas were frequently found, and where demyelination and breaking down of axons were still in progress scavenger cells, loaded with fat droplets, were noticeable. Evidence of reaction of glia cells in the parts that were damaged was encountered at times, mostly without appreciable increase of glial fibers.

*Summary.* Rats submitted to repeated blunt impacts on the head, the strength of each of which was insufficient to cause any immediate or late ill effects, frequently revealed cumulative effects as shown by unconsciousness, at times followed by death or by persisting changes in behavior. A certain correspondence was found between the response to the trauma during life and the amount and degree of cerebral damage at post mortem examination, which consisted mainly of degenerative changes in neurons detected by present histological methods.

## 14778 P

## Microscopic Neuronal Injury in Rats Submitted to Concussive Head Trauma Under Different Mechanisms.

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Preliminary experiments in an investigation on the effects of repeated minimal impacts on the head led to the study of a number of brains of animals (68) recovering from a short period of unconsciousness after receiving a single concussive blow. Using a trauma of the same momentum (mass 567 g, velocity 345 cm/sec), half of the animals were made to strike the moving head against a stationary object and the other half were struck by a moving object on the stationary head. Although no differences were seen in the immediate effects in the two series (all animals being made unconscious by the blow for a period ranging from 10 seconds to 15 minutes), in view of the possibility of different morphological patterns resulting from the two different mechanisms of trauma, a comparative study of this material seemed of value.

*Observations.* At postmortem examination, no evidence of skull fracture was found in any case, and in all but one, in which petechial hemorrhages were seen in both the pons and the bulbar region, the gross inspection of the brains and even the study of the hematoxylin-eosin stained sections failed to reveal any remarkable change, except for an occasional vascular engorgement and for some doubtful signs of edema of the brain matter. However, when the stains proper for the nervous system elements were applied, definite neuronal changes were seen. Regardless of the mechanism of trauma these changes had a wide distribution, involving the cerebral