areas around the infarct in which collateral circulation had presumably been established and a degree of recovery from ischæmic damage rendered possible. The fine structural appearances we found replacing normal cell architecture are those known to occur in the developing embryonic heart-muscle cell [8-10] and the changes in ribosomes, rough endoplasmic reticulum, and Golgi complex are those seen when active protein synthesis is proceeding.[11] Biochemical studies have also shown an increase in protein synthesis in tissue at the edge of a myocardial infarct though the site of these changes—whether in myocardial cells, fibroblasts or leucocytes—was not identified.[12,13]

We conclude that after ischæmic damage resulting in death of part of the myocardial cell, some regeneration of that cell may occur, and that the process may continue for 3 weeks at least. These findings are relevant to an understanding of the physiology of the myocardial cell and its response to injury. Since factors which encourage regeneration should result in better residual myocardial function, our observations emphasise the need to develop methods for preserving satisfactory Po_2 levels in the border-zone of a clinical myocardial infarct.

This study was supported by Grants from the National Heart Foundation of Australia and Merck Sharpe and Dohme, Sydney. We thank Miss Elizabeth Fennell and Mrs. P. Wilde for technical and secretarial assistance.

Requests for reprints should be addressed to D. E. L. W., Department of Medicine, Prince Henry Hospital, Little Bay, New South Wales 2036, Australia.

REFERENCES

1. Jennings, R. B., Baum, J. H., Herdson, P. B. *Archs Path.* 1965, **79**, 135.
2. Herdson, P. B., Sommers, H. M., Jennings, R. B. *Am. J. Path.* 1965, **46**, 367.
3. Wartman, W. B. *Ann. N.Y. Acad. Sc.* 1969, **156**, 7.
4. Korb, G., Totović, V. *ibid.* p. 48.
5. Jennings, R. B., Sommers, H. M., Herdson, P. B., Kaltenbach, J. P. *ibid.* p. 61.
6. Wilcken, D. E. L., Brender, D., Shorey, C. D., MacDonald, G. J. *Science*, 1967, **157**, 1332.
7. Wilcken, D. E. L., Brender, D., MacDonald, G. J., Shorey, C. D., Hinterberger, H. *Circulation Res.* 1967, **21**, suppl. 3, p. 203.
8. Virágh, S. *in* Proceedings of the Third European Regional Conference on Electron Microscopy (edited by M. Titlvach); vol. B, p. 95. Prague 1965.
9. Heuson-Stiennon, J. *J. Microscopie*, 1965, **4**, 657.
10. Manasek, F. J. *J. Cell Biol.* 1968, **37**, 191.
11. Caro, L. G., Palade, G. E. *ibid.* 1964, **20**, 473.
12. Gudbjarnason, S., De Shryver, C., Chiba, C., Yamanaka, J., Bing, R. J. *Circulation Res.* 1964, **15**, 320.
13. Bing, R. J., Gudbjarnason, S., Tschopp, H., Braasch, W. *Ann. N.Y. Acad. Sci.* 1969, **156**, 583.

Hypothesis

CHEMICAL BASIS OF EPILEPSY

HAROLD HILLMAN
Biological Sciences Department, University of Surrey

Summary Epilepsy attacks may be caused by increased permeability to sodium and potassium ions of membranes in a localised group of cells. The resultant increase in extracellular potassium causes other cells to fire. Synthesis of high-energy phosphate compounds is needed to restore ionic gradients and allow affected brain cells to recover.

I SHOULD like to suggest that an attack of epilepsy is caused by an increased permeability to sodium and potassium ions of the membranes of a localised group of cells, adjacent to a motor area. This increased permeability permits reduction of the transmembrane ionic gradients, and the group of cells fires. The resultant increase in extracellular potassium-ion concentration causes other cells in the region to fire, and the focus spreads. The resulting massive discharge leaves that part of the brain electrically inert, and depletes the " high energy " compounds necessary to recreate the ionic gradients across cell membranes. These phosphate compounds are resynthesised, and can provide the energy to pump the sodium out of the cells, and the potassium into them, thus allowing the affected region of the brain to recover.

During epileptic seizures, single cells in the cerebral cortex fire rapidly, with a partial depolarisation after the seizure, though without a change in threshold to firing.[1-3] During spreading depression, depolarisation has been observed.[4] Electrical stimulation of the " brain slab " in cats induces a " burst " response which spreads from the stimulated area.[5] Electrical stimulation of cerebral slices causes influx of sodium ions, efflux of potassium ions,[6,7] and depolarisation of cellular elements within them: the depolarisation is prevented by phenobarbitone,[8] a drug commonly used to prevent epileptic attacks.[9] The efflux of potassium ions [7,8] causes sufficient external accumulation to depolarise the cellular elements.[10,11] During this depolarisation, the cells would fire. If then, there was a local increase of permeability of a group of cells, the focus could spread to a motor area of the cortex, which would then generate limb movement.

In 1660 Boyle showed that acute hypoxia can cause convulsions.[12] Rats dying of excess anæsthesia or coal-gas poisoning have convulsive movements.[13] Carbon-monoxide poisoning in man is characterised by convulsions.[14] Low oxygen tension depolarises mammalian cortical and spinal cells in vivo [15,16] and in vitro [10,17]; it decreases the ion gradients in cerebral slices.[18,19] A reversible loss of polarisation develops in isolated Deiters' neuron-cell bodies of rabbits in this condition.[20] Lowering the glucose concentration in which cerebral slices are incubated decreases their polarisation [10,11,17] and their cation gradients.[21,22] The spread of excitation due to electrical stimulation on the surface of the cortex of mammals has been widely studied.[23-26] The time-courses of recovery from epileptic attacks and depolarisation of cerebral slices due to electrical stimulation are similar.[8] A relatively low substrate or oxygen supply would occur if the normal blood-supply to a small part of the brain were temporarily or permanently restricted; flashing lights, which may induce an epileptic attack, would cause depolarisation throughout the visual system, which would predispose to repetitive firing.[1-3] Thus, such conditions could induce a depolarising focus.

Cerebral abscesses or scars can act as foci of epileptic discharges; since crushing depolarises nerve ends [27] it would be expected that the poisoned, hypoxic, or

compressed cells adjacent to abscesses or scars might be continual depolarising foci. All the conditions mentioned (i.e., electrical stimulation, high extracellular potassium ion, low oxygen tension or glucose concentration, damaged tissue) if occurring locally might well lower the cell polarisation of individual cells of a group from about 70 mV to about 60 mV. If the firing threshold were, say, 50 mV they would normally require a stimulus depolarising them by 20 mV; in this state of lowered polarisation, a stimulus causing a further decrease in polarisation of only 10 mV would make them fire.

This scheme assumes that results from experiments on epileptic foci, the cerebral cortex of anæsthetised animals, brain " slabs ", cerebral-cortex slices in vitro, and isolated neuron-cell bodies, are mutually applicable, and thus the effects of agents such as electrical stimulation, high medium potassium ion, hypoxia, and so on are similar in all of them. Besides its theoretical implications, the usefulness of this hypothesis could be tested by the expectation that any drugs or agents which might increase the extracellular-intracellular potassium and sodium ion gradients (e.g., by increasing the substrate or oxygen available) might usefully be tested for their efficacy against epileptic attacks.

Requests for reprints should be addressed to the Biological Sciences Department, University of Surrey Annex, 14 Falcon Road, London S.W.11.

REFERENCES

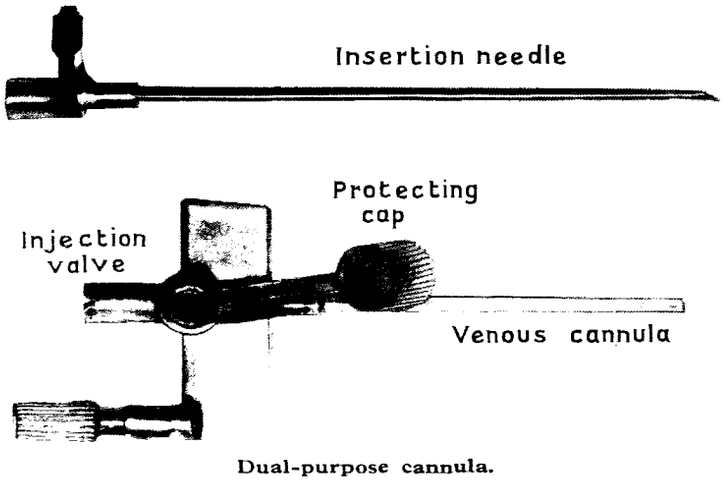
1. Li, C. L., Jasper, H. *J. Physiol., Lond.* 1953, **121**, 117.
2. Kandel, E. R., Spencer, W. A. *Epilepsia*, 1961, **2**, 63.
3. Sawa, M., Maruyama, N., Kaji, S. *Electroenceph. clin. Neurophysiol.* 1963, **15**, 209.
4. Aquino-Cias, J., Belceva, C., Bures, J., Fifkova, E. *Proc. Czech. physiol. Soc., Olomouc*, 1965.
5. Burns, B. The Mammalian Cerebral Cortex; p. 14. London, 1958.
6. Cummins, J., McIlwain, H. *Biochem. J.* 1961, **79**, 330.
7. Bachelard, H., Campbell, W. J., McIlwain, H. *ibid.* 1962, **82**, 225.
8. Hillman, H., Campbell, W. T., McIlwain, H. *J. Neurochem.* 1963, **10**, 325.
9. Conybeare, J., Mann, W. N. Textbook of Medicine; p. 957. Edinburgh, 1961.
10. Li, C. L., McIlwain, H. *J. Physiol., Lond.* 1957, **139**, 178.
11. Hillman, H., McIlwain, H. *ibid.* 1961, **157**, 263.
12. Boyle, R. New Physico-mechanicall Experiments Touching the Spirit of Air, and its Effects. Oxford, 1660.
13. Feldman, H., Hillman, H. *Br. J. exp. Path.* 1969, **50**, 158.
14. Lennox, W. C. Epilepsy and its Related Disorders; p. 743. London, 1960.
15. Li, C. L. *J. Physiol., Lond.* 1955, **130**, 96.
16. Kilmoddin, G. M., Skoglund, C. R. *Acta physiol. Scand.* 1959, **45**, 1.
17. Hillman, H. *J. Neurochem.* 1961, **8**, 257.
18. Krebs, H. A., Eggleston, L. V., Terner, G. A. *Biochem. J.* 1951, **48**, 530.
19. Pappius, H. M., Elliott, K. A. C. *Can. J. Biochem. Physiol.* 1956, **34**, 1053.
20. Hillman, H., Hyden, H. *J. Physiol., Lond.* 1965, **177**, 398.
21. Joanny, P., Hillman, H. *J. Neurochem.* 1963, **10**, 655.
22. Joanny, P., Hillman, H. *ibid.* 1964, **11**, 413.
23. Chang, H. S. *J. Neurophysiol.* 1951, **14**, 1.
24. Liddell, E. C. T., Phillips, C. G. *Brain*, 1952, **75**, 510.
25. Phillips, C. G. *Q. Jl exp. Physiol.* 1956, **41**, 60.
26. Purpura, D. P., Girado, M., Grundfest, H. *Proc. Soc. exp. Biol., N.Y.* 1957, **95**, 91.
27. Hodgkin, A. L., Huxley, A. F. *J. Physiol., Lond.* 1945, **104**, 176.

Methods and Devices

DUAL-PURPOSE CANNULA

IAN F. PYE
WILLIAM DEAVILLE JOHN SILK
Coronary Care Unit, City General Hospital, Stoke-on-Trent

IN a coronary-care unit a variety of drugs may need to be given intravenously, especially in the first 72 hours after an infarction. In many centres it is standard practice during this critical period to set up an intravenous infusion, or insert some form of indwelling cannula to provide a readily available intravenous route in case of an emergency, such as cardiac arrest or ventricular tachycardia. The disadvantages of a continuous infusion are that it requires frequent attention, and there is a risk of circulatory overload with unnecessary fluid. A dual-purpose cannula suitable for administering intravenous injections and for rapid connection to an infusion seemed desirable, and we now record our experience in seventy-five cases with a disposable ' Venflon ' cannula.



Dual-purpose cannula.

The cannula (see photograph) is made of ' Teflon ' and allows intermittent intravenous injections through a portal on its upper surface via a one-way valve. An infusion can be connected to the end of the cannula which is otherwise occluded by a Luer fitting plug. The insertion needle is discarded after venepuncture. The cannula is inserted immediately on admission by direct puncture, usually of a forearm vein, and secured by ' Elastoplast '. 250 units of heparin are injected through the injection valve and repeated 24 hourly to maintain patency. The cannulæ were left in situ for periods from 24–120 hours and all were patent on removal; in thirty-seven cases this was after more than 96 hours and in twenty-three cases more than 72 hours. The other fifteen cannulæ were removed before seventy-two hours, either because the patient died or the diagnosis of myocardial infarction was not confirmed. Two patients had a superficial thrombophlebitis of the forearm and one had an infected puncture site.

The device seems to possess several advantages in the intensive-care situation:

(1) Ease of insertion, and high degree of tolerance by the patient who can use his hand freely.

(2) No need for repeated venepuncture.

(3) Availability of immediate intravenous access beyond the post infarction period without a continuous infusion.

(4) Availability of intravenous route for drugs such as lignocaine or isoprenaline, separately or concurrently with fluids (e.g., sodium bicarbonate in cardiac arrest).

(5) Low incidence of superficial thrombophlebitis or clinical infection.