Operation was done in 130 cases, 34 being examples of combined mitral and aortic stenosis.

The mortality of operation need be no more than 10-15%. A good result was obtained in about 70% of survivors. The mortality will always be high if operation is deferred until features of heart failure have appeared.

The patients included in this study were almost all operated on in collaboration with Drs. Maurice Campbell, Paul Wood, Charles Baker, and Ronald Gibson; I am indebted to them all. I am also grateful for the invaluable help of various colleagues in the investigations before, during, and after operation. Fig. 8 is from records made by Dr. P. Fleming, and Figs. 1, 2, 3, 4, 6, and 9 are from records made by Dr. R. Gibson. I am grateful to Dr. Lawson McDonald for the arterial pulse tracing in Fig. 7.

REFERENCES

- Bailey, C. P., Bolton, H. E., Jamison, W. L., and Nichols, H. T. (1954). *Circulation*, **9**, 22.
 ——— Nichols, H. T., Jamison, W. L., and Litwak, R. C. (1956). *J. thorac. Surg.*, **31**, 375.
 ——— Ramirez, H. P. R., and Larzelere, H. B. (1952). *J. Amer. med. Ass.*, **150**, 1647.
 Baker, C. G., and Campbell, M. (1956). *Lancet*, **1**, 171.
 Björk, V. O., Malmström, G., and Uggla, L. G. (1953). *Ann. Surg.*, **138**, 718.
 Brock, R. C. (1950). *Guy's Hosp. Rep.*, **99**, 236.
 ——— (1956). *Proc. roy. Soc. Med.*, **49**, 347.
 ——— and Campbell, M. (1950). *Brit. Heart J.*, **12**, 377.
 ——— and Fleming, P. R. (1956). *Guy's Hosp. Rep.*, **105**, 391.
 ——— Milstein, B. B., and Ross, D. N. (1956). *Thorax*, **11**, 163.
 ——— and Ross, D. N. (1955). *Guy's Hosp. Rep.*, **104**, 99.
 Fell, E. H. (1955). In *International Symposium on Cardiovascular Surgery*. Detroit, p. 318. Philadelphia.
 Fleming, P. R., and Gibson, R. V. (1957). *Thorax*, **12**, 37.
 Harken, D. E. (1955). In *International Symposium on Cardiovascular Surgery*. Detroit, p. 315. Philadelphia.
 Lewis, F. J., Shumway, N. E., Niazi, S. A., and Benjamin, R. B. (1956). *J. thorac. Surg.*, **32**, 481.
 Lewis, T. (1933). *Diseases of the Heart*. London.
 Likoff, W., Berkowitz, D., Denton, C., Goldberg, H., and Reale, A. (1955). *J. Amer. med. Ass.*, **157**, 1367.
 Lillehei, C. W., DeWall, R. A., Gott, V. L., and Varco, R. L. (1956). *Dis. Chest*, **30**, 123.
 Logan, A., and Turner, R. (1954). *Lancet*, **1**, 1091.
 Marquis, R. M., and Logan, A. (1955). *Brit. Heart J.*, **17**, 373.
 Matthews, M. B., Medd, W. E., and Gorling, R. (1955). *British Medical Journal*, **2**, 759.
 Milstein, B. B., and Brock, R. C. (1954). *Guy's Hosp. Rep.*, **103**, 213.
 Nadas, A., and Ongley, D. A. (1956). Second European Cardiology Congress, Stockholm.
 Smithy, H. G., and Parker, E. F. (1947). *Surg. Gynec. Obstet.*, **84**, 625.
 Souttar, H. S. (1925). *British Medical Journal*, **2**, 603.
 Tuffier, T. (1913). *Trans. Int. Congr. Med.* (London, 1914), sect. vii, surgery, pt. 2, p. 249.
 Uricchio, J. F., Litwak, R., and Bailey, C. P. (1955). *Circulation*, **12**, 785.

MENTAL PERFORMANCE IN CHRONIC ANOXIA*

BY

RAYMOND GREENE, M.A., D.M., F.R.C.P.

Formerly Vice-President of the Alpine Club

No one has ever had the opportunity to observe the unalloyed effects of prolonged severe oxygen deficiency in man. In physical illness there are always impurities present: in anaemia, the cause of the anaemia; in pulmonary disease, the toxic effects of the causative organism or of the secondary invaders; even in cardiac disease, such confusing factors as the presence of cerebral arteriosclerosis. At great altitudes the complicating factors are numerous. The most important is probably the psychological make-up of the climber. A full discussion of the problem would lead the inquirer into such private fields as his subject's reason for going to the mountains at all. The Walter Mitty complex, so well described by that excellent psychologist James Thurber, is probably the common thread which runs through all our tangled motives for being mountaineers, but in many of us some of the motives are less worthy of

respect, and in consequence psychological breakdowns may occur and may have effects upon the other members of a party which may wrongly be ascribed to what on Everest in 1933 was vulgarly described as "alt."

Such considerations urge caution in attacking the question of the mental effects of chronic anoxia along the usual anecdotal lines. A description of the manic behaviour of A on Everest or the depressive interlude experienced by B on Kangchenjunga must be sceptically examined for possible psychological, as opposed to physiological, causes. Unfortunately the very proper loyalty which censors the reports of every returning mountaineer makes it impossible to obtain a sufficiently detailed description of the mental atmosphere of the party as a whole or the pattern of behaviour of individual members.

Confused though the problem is by psychological considerations and by such additional complications as wind and weather, nutrition, and technical mountaineering difficulties, we are not entirely without guidance in our search for essentials. We can look for the common factors in the conditions of chronic anoxia due to physical disease and chronic anoxia due to altitude. Bearing in mind that the clinical picture is modified by different impurities, we may justifiably assume as a working hypothesis that common factors are the result of chronic anoxia pure and simple. We can administer a further test by studying acute anoxia, whether it be anoxic, anaemic, stagnant, or histotoxic. Broadly speaking, a chronic condition produces signs and symptoms similar to those of an acute condition, modified by their being milder, more prolonged, and in consequence admixed with the syndrome produced by the adaptive reactions of the body, which, in the acute condition, have not had the necessary time to develop.

Chronic Anoxia

It is convenient first briefly to consider the effects upon the mind of chronic anoxia studied at moderate altitudes in health and at sea-level in other forms of anoxic anoxia (as in pulmonary disease); in anaemic anoxia (as in pernicious or Addisonian anaemia); and in stagnant anoxia (as in cardiac failure).

Perhaps the most reliable information bearing on our present purpose is that which has been obtained by the observation of man during prolonged residence at moderate altitudes. When I was in Darjeeling, which lies at about 7,000 feet (2,130 metres), I found a fairly general impression that those who stayed there for a year or more without a break at lower levels, often became somewhat irritable, and I have heard the same story from doctors practising in Johannesburg, which lies at a similar level. If we go twice as high, to 14,000 feet (4,270 metres), we have the observations of Barcroft (1925) at Cerro de Pasco. Mental tests disclosed nothing; and Barcroft wrote:

"Yet I am not prepared to admit that our mental capacity was the same at Cerro as it is here. All the party will agree, I believe, that the reason why the mental tests failed to reveal the difference was because our mental disability was of too subtle a character to be revealed by somewhat simple tests than because the fitness of our minds was unimpaired. It is possible to force oneself to do good work even though the test measures the quality of work done; but were it ideal it would also measure the degree of concentration brought to bear upon the task." [One is reminded of the interesting experiment conducted many years ago by some young gentlemen of a famous medical school who by constant practice trained themselves to perform perfectly, even in a state of severe alcoholic intoxication, all the tests employed by the police for drunkenness.] "Apart from the actual processes of addition, subtraction, etc., there seemed to be an unwonted difficulty in stating a sum at Cerro if it were not of a quite simple character. The Van Slyke method of gas analysis

*Read at a Symposium at the Royal Society, Burlington House, London, on January 28, 1954.

demands the application of some rather complicated tables of correction to the gas volumes as actually measured. These corrections loomed large at Cerro altogether out of proportion to their real difficulty. . . ."

Barcroft's observations on the inability of mental tests to show mental deterioration at 14,000 feet (4,270 metres) were confirmed by Hingston (1924) at 21,000 feet (6,400 metres). No deterioration in actual performance was demonstrable. Yet such a deterioration exists. I well remember the difference in effort needed to take samples of alveolar air at Base Camp on Everest (17,000 feet—5,180 metres) and at Camp V (25,600 feet—7,800 metres). At Base Camp it was an almost automatic process performed in a few seconds. At Camp V it needed a conscious effort of concentration.

Turning to other causes of chronic anoxic anoxia, one finds a dearth of recorded observations and there is equal silence on the subject of mental performance in chronic anaemic anoxia, though Thomas Addison himself noted personality changes in some of his patients.

In stagnant anoxia, such as that due to chronic congestive cardiac failure, observations on the mental processes have been numerous and have been correlated with the arterio-venous oxygen difference. The subject has been reviewed by Himwich (1951). Neuroses are common in cardiac failure, especially confusion, delusions of persecution, and exacerbation of previous anxiety states. It is difficult for the hospital doctor (by whom the majority of such observations are recorded) to assess such changes. He cannot compare the present mental state of his patient with the past. In general practice such observations are easy but have never been recorded. My own impression is that in the chronic anoxia of cardiac failure and advanced pulmonary disease one sees an accentuation of a previous mental abnormality rather than the creation of a new one. The man one has known for years as a well-balanced, placid, good-tempered, co-operative patient retains these characteristics in a state of chronic anoxia due to illness. One feels that one of the effects of the illness is to strip the veneer off a man and expose the quality of his mind naked to the world. I think that the same thing happens in alcoholic intoxication and in the chronic anoxia of great altitudes. The effects on the mind of a decrease in the A-V oxygen ratio are superimposed on individual characteristic patterns of behaviour.

Acute Anoxia

In acute anoxia we can study a relatively pure process, unaffected by the protective reactions of the body. This may be done at great altitudes in balloon ascents or in low-pressure chambers, and during carbon monoxide poisoning. Moreover, as there is good reason to believe that what we observe in acute anoxia is in fact the result of diminished cerebral metabolism, we may study its effects by analogy and in good experimental conditions, during myxoedema or hypoglycaemia, whether spontaneous, accidental (as in diabetics after an overdose of insulin), or purposeful (during the treatment by means of insulin of various mental abnormalities).

Haldane's description of acute anoxic anoxia is well known (Haldane and Priestley, 1935). It is worthy of fuller quotation than space will allow. He draws attention to several effects which are observable during chronic anoxia—the dulling of the senses and intellect, the loss of memory and of sane judgment, and the tendency to uncontrolled emotional outbursts. He comments on the likeness which exists between the effects of anoxaemia and of alcohol, a similarity stressed also by Barcroft and by Hingston. Yet these effects are demonstrated very unevenly. An extreme example of mental and physical control was that of Coxwell, who with Glaisher ascended in 1862 in a balloon to 29,000 feet (8,840 metres). Glaisher was by this time unconscious, but Coxwell was still able to clamber into the rigging to free a tangled rope and thus to save his own and Glaisher's life—an interesting fact in view of recent arguments about the necessity of oxygen apparatus on Everest.

More recently McFarland (1938) has described the results of acute exposure of human beings to low oxygen pressures. No change is observed below about 12,000 feet (3,660 metres), when the memory for recent events becomes slightly impaired. At about 14,000 feet (4,270 metres) changes in mood may be observed, differing from one individual to another, and there may be lassitude or euphoria. At 18,000 feet (5,490 metres) sensory perception is decreased, the field of attention is narrowed, irrational behaviour may be manifest, and judgment is impaired. Above 20,000 feet (6,100 metres) reaction times are slowed, awareness of the passage of time becomes inaccurate, and explosive emotional outbursts may occur.

The study of carbon monoxide poisoning and, more especially, of hypoglycaemia has given us much information about the processes involved. As the schizophrenic patient sinks into coma under the influence of insulin, his physical signs denote a steady deterioration of cerebral control from the cortex downwards and it is possible to watch the patient's bodily control dropping in phylogenetic stages from the cortex, via the diencephalon and the upper medulla to the lower medullary region. During recovery the development of the brain is recapitulated. Each area of the brain during the process called by Hughlings Jackson "dissolution" uses, as hypoglycaemia advances, a steadily decreasing amount of oxygen, and when the oxygen needs of each part of the brain are separately examined it is found that the higher the part of the brain examined the higher are its demands. It follows that the more avaricious parts are the first to succumb. A relatively mild deficiency affects only the newer parts of the brain, and at the other end of the scale a very severe deficiency is needed to bring to a final end the function of the medulla.

In mild acute anoxia and the chronic anoxia of great altitudes this process stops at the first stage, the abolition in part of cortical control. Rarely indeed does the mountaineer evince the sham rage of the decorticated cat, but he may often come very near to doing so. There is reason to believe that the stratifications of the brain as a whole are reflected in the laminations of the highest centres. An analogy with the effects of alcohol in excess is not strictly sound, because although alcohol reduces brain metabolism very much as do anoxia and hypoglycaemia, it has probably another and separate activity. Nevertheless Barcroft's evidence, which I can support from my personal observations, strongly suggests that the analogy is a useful one. Within the cortex, it is the higher control which is first lost, the inhibitions imposed by recent training preceding in their exit those more deeply embedded in childhood. A similar though cruder sequence is seen during the slow induction of anaesthesia by barbituric acid derivatives. One sees first euphoria, then loss of inhibitions, ineptitude in obeying commands, loss of mental concentration, and finally loss of consciousness.

Great Altitudes

We must now turn to a consideration of the more complex phenomena of mental processes in man in the special circumstances of high mountains, and attempt to recognize changes in performance which reflect the changes of acute anoxia and of the milder and less complicated circumstances of chronic anoxia in human illness. The common factors may, *ex hypothesi*, be accepted as due to severe chronic anoxia and not to meteorological or strictly psychological causes. The earliest observations are those of Hingston (1924).

"High altitudes affect the operations of the mind. One member was confident of a dulling of the will power, a diminution in the strength of purpose, with less and less desire to reach the summit the farther he made the ascent. Somervell describes a lack of observance at and above 25,000 ft. (7,620 metres). Bruce records an enfeeblement of memory. He found an effort in recalling previous events. Above 23,000 ft. (7,010 metres) his ideas became increasingly inaccurate. It was necessary for him to record them immediately, as otherwise they would become forgotten or distorted. I think everyone experienced some mental

lassitude. Though the mind was clear, yet there was a disinclination for effort. It was far more pleasant to sit about than to do a job of work that required thought. . . . Though mental work is a burden at high altitudes, yet with an effort it can be done. One physiologist has said that sustained mental work is out of the question at anything over 10,000 ft. (3,050 metres). We certainly could not agree with this. Those who have read Norton's despatches to *The Times*, especially one dictated at Camp III, when he was burdened with anxiety and partially blind, will admit that this effort from 21,000 ft. (6,400 metres) was not a bad intellectual performance. The main effect of altitude is a mental laziness which determination can overcome."

Personal Observations

May I turn now to a few sketchy observations of my own? It is well that I recorded them at the time. It may in itself be significant that when I read my diary again after an interval of 20 years I found that I had completely forgotten a lot of what had happened under my eyes on the upper part of Everest, though the incidents below about 20,000 feet (6,100 metres) still seemed fresh in my mind.

Only one member of the expedition was seriously affected at Base Camp (17,000 feet—5,180 metres). Mental lassitude assailed him so severely that he gradually withdrew himself from the day-to-day work of the camp. He ceased to take any interest in the job which had been assigned to him, and his work was gradually taken over by other people without any protest or resistance. He ultimately improved and succeeded in reaching the North Col, but he never pulled his weight in the Expedition again. No one else showed any change in mental performance below the North Col (23,000 feet—7,010 metres), when several people began to complain of nightmares. Two members became argumentative, over-critical, and, if opposed, surly. One of these made a gradual recovery, but the other, after an ascent to 25,000 feet (7,620 metres), became extremely ill-tempered and suffered from the delusion that he was severely frost-bitten. In fact, he was not frost-bitten at all, but he spent several days at Base Camp refusing to leave his tent.

A curious case which I am inclined to ascribe to other causes than pure chronic anoxia was that of a member who acquitted himself well up to the North Col, the highest point planned for him. On his return to lower levels he developed a severe paranoid psychosis from which he did not recover until a few days before his return to Darjeeling. I think that here anoxia was only a contributory factor. He was a man whose physical and mental fitness were below the level demanded but who from a sense of duty had driven himself to breaking-point.

Apart from these examples, no mental changes were observed except in those who climbed above 27,000 feet (8,230 metres). All of these had "waking dreams" which took the form of terrifying nightmares except in the case of Frank Smythe, who recorded his impressions in his book *Camp 6*. He was convinced, when climbing alone, and of course without oxygen equipment, at about 28,000 feet (8,530 metres), that he had with him a friendly companion, to whom at one point he offered a sandwich. He also had visual hallucinations, seeing above the ridge of the mountains some curious dark bodies which came to be known as "Frank's pulsating teapots." Yet his judgment otherwise was quite unimpaired. At 28,100 feet (8,565 metres), with the summit less than 1,000 feet (305 metres) above him, he was able soberly to consider the pros and cons of continuing, weighing his feeling of physical fitness and the early hour against the bad condition of the snow, and coming to the unwelcome conclusion that he must return. Smythe never suffered from the irritability which occasionally appeared in all the rest of us who went high. It seemed that chronic anoxia increased his placidity. At low altitudes a little inclined to take offence, at great ones he emanated serenity and an infectious happiness.

Indeed, those who reached the highest points were, it seemed, less affected by ill-temper, perhaps because even ill-temper requires a certain level of oxygen tension to develop. They may by this time have reached a condition

of fatuous good-temper. This was certainly true of one of us, who after his return from the higher reaches was confused, somewhat aphasic, and disinclined to talk, preferring to sit in silence, benignly contemplating his surroundings. The failure of memory which has so often been described affected us very unequally. One man was very conscious of this at the time. He said his mental capacity was 25% of normal. He forgot that his job was the exploration of the Second Step, though this had been his much-discussed assignment for weeks. Happily his companion remembered.

Another effect of high altitudes which can be recognized as an effect of oxygen deficiency rather than of psychological and mental stress is a dulling of the special senses, for this occurs very noticeably in acute oxygen deficiency. This was first observed by Paul Bert (1943) and confirmed by Haldane and others (1919). The dulling is not as a rule observed: it is the return of brightness to light and colour, and of loudness to sound, which strikes one when the oxygen supply is increased. I wrote of this when returning from the summit of Kamet (25,447 feet—7,756 metres), in 1931 (Greene, 1932).

"In the neighbourhood of our old Camp One the snow began to fall less thickly, and far ahead we could see the end of the East Kamet Valley, and the dark and snow-streaked rock peaks lying above Base Camp. It was at this point—at about, I suppose, 16,500 feet (5,030 metres)—that a change came over my feelings. Haldane has written how, in his experiments on the effects of low air-pressure, he sat in his steel chamber with the pressure gradually rising towards the normal: and how, at a certain level, the electric light glowed suddenly more brightly. At first he thought that the current had been increased, but later he came to realize that the change was in himself and not in the current. For me, shut in no steel chamber, but walking slowly down the East Kamet Glacier, depressed by wind and weather and painful feet, the whole aspect of life as suddenly changed. I began once more to appreciate the pleasures of the senses. The snow was whiter and more scintillating. When, little by little, patches of sky began to show between the banks of cloud, they seemed a brighter blue than the skies of Kamet. One began to hear and to smell more acutely. It is clear that not only are one's senses dulled by lack of oxygen, so that the light in the steel chamber becomes dull and the Himalayan sky less blue, but that all one's mental processes suffer a like fate. Especially, at great heights one does not gloat over one's pleasures. One loses, as Goethe has put it, 'the capacity to submit to impressions; to be delighted, touched, and exalted.' But now this capacity was suddenly restored."

Conclusions

It is now possible to sift the observations of Everest doctors on the mental performances of their parties and to trace their similarity with those observed during anoxia in other circumstances. The following facts emerge.

1. Chronic anoxia affects different people very differently, both quantitatively and qualitatively. Some men are remarkably resistant, showing within the limits of the "experiment" little change at all. Those who show definite changes are affected very much as they are by alcoholic intoxication, the protective skins of their essential mental make-up being stripped off onion-fashion, the more recently acquired inhibitions being the first to go.

2. Memory is seriously affected, though to different degrees in different individuals.

3. The capacity accurately to perform mental work is affected. Tests hitherto performed have been too easy and have failed to show this, but more concentration has been needed in their performance at great altitudes, and harder tests might be employed in future.

4. Emotional instability may be severe. This usually takes the form of irritability. The tearfulness described by Barcroft does not occur in other descriptions than his and is probably the result of mental fatigue rather than of anoxia. Conversely, many travellers' tales of strange behaviour at great altitudes should be discounted because of a lack of similarity to mental changes occurring in acute anoxia and in chronic anoxia due to other causes.

May I end by quoting with sympathy the words of Mosso (1898)? "It is my wish to find some man with a hole in

his skull who would have been willing to come with me on the Monte Rosa Expedition, but I was not successful in my search. Some other physiologist will, I hope, be luckier."

REFERENCES

- Barcroft, J. (1925). *The Respiratory Function of the Blood*, Part I. Cambridge.
 Bert, P. (1943). *Barometric Pressure*. Columbus, Ohio.
 Greene, R. (1932). In *Smythe's Kamet Conquered*. London.
 Haldane, J. S., Kellas, A. M., and Kennaway, E. L. (1919). *J. Physiol. (Lond.)*, 53, 183.
 — and Priestley, J. G. (1935). *Respiration*, p. 200. Oxford.
 Himwich, H. E. (1951). *Brain Metabolism and Cerebral Disorders*. Baltimore.
 Hingston, R. W. G. (1924). *Geogr. J.*, 65, 4.
 McFarland, R. A. (1938). Dept. of Comm., Bureau of Air Comm., Report No. 13.
 Mosso, A. (1898). *Life of Man in the High Alps*. Translated from second Italian edition. London.

PRODUCTION OF FIBRILLATION IN ISOLATED ATRIA OF RABBIT HEART

BY

W. C. HOLLAND, M.D.

AND

J. H. BURN, M.D., F.R.S.

From the Department of Pharmacology, University of Oxford

The atria of the hearts of small animals can be dissected from other tissue and suspended in a bath containing some modification of Ringer's solution, and in this bath they maintain their rhythmic contractions. A few observations have been made of the production of arrhythmias in such preparations. Dawes and Vane (1951) studied the guinea-pig atria at 37° C., stimulating them electrically at a rate slightly greater than the spontaneous rate. They observed that if a test-pulse was thrown in just outside the absolute refractory period, the atria often responded by repetitive discharges at a frequency much greater than the normal rate of beat. These discharges continued for periods up to one hour. DiPalma and Mascatello (1951) made similar observations in cat atria at 29° C., though the repetitive discharge was of shorter duration. West, Turner, and Loomis (1954), in the course of studies on excitability and conduction time, noted the occurrence of arrhythmias when the interval between two stimuli was near the absolute refractory period; these lasted from a few seconds to several minutes, and they said that the arrhythmias occurred regularly in the presence of acetylcholine.

Burn, Vaughan Williams, and Walker (1955) observed that during the infusion of acetylcholine into the heart-lung preparation of the dog stimulation of the right atrium resulted in fibrillation, which persisted when stimulation ceased. The fibrillation continued so long as acetylcholine was infused, and could be terminated at will by stopping the infusion or by injecting atropine. In a later paper

FIG. 1.—Broken lines show a glass tube, through which a pair of shielded and insulated wires run, terminating in platinum electrodes. The two limbs of the U are joined by a solid piece of glass, sloping as shown, to which the lower ends of the atria are attached. The electrodes pierce the atria.

Burn, Gunning, and Walker (1956) showed that the fibrillation was also stopped by a slow infusion of KCl.

We now describe the production of fibrillation in the isolated atria of the rabbit by stimulation in the presence of acetylcholine.

Method

Rabbits weighing 2–3 kg. were used. They were stunned by a blow on the head, and the hearts were removed and placed in Ringer's solution of the following composition: NaCl, 9 g.; KCl, 0.4 g.; CaCl₂, 0.24 g.; NaHCO₃, 0.5 g.; dextrose, 2 g.; distilled water, 1 litre. The atria were dissected free from fat and other tissue, attached to an electrode (see Fig. 1) designed by Mr. O. B. Saxby, of this department, and suspended in a bath of the solution described which was aerated with oxygen and maintained at 30–31° C. A mechanical record was taken on a kymograph. The atria were stimulated by square wave pulses of 0.75 msec. duration and of 6–10 volts strength. Surface electrograms were recorded from the stimulating electrodes on a Cossor machine (model 1314).

Production of Arrhythmia

In the initial experiments, atria, suspended in the bath, were stimulated at frequencies varying from 200 to 1,200 a minute for different periods. In all preparations the normal rhythm returned immediately on cessation of stimulation. Low concentrations of acetylcholine had very little effect on the sequence of events. With concentrations greater than 3×10^{-4} g. per ml. repetitive charges of brief duration, from 2 to 5 seconds, were occasionally observed after stopping the stimulation, but persistent arrhythmia was not seen.

In further experiments the concentration of KCl in the solution was reduced to one-quarter (100 mg. per litre). Stimulation still failed to produce arrhythmia in the presence of low concentrations of acetylcholine, but, when the concentration was greater than 3×10^{-4} g. per ml. and the frequency of stimulation was greater than 600 a minute, arrhythmia then persisted, as demonstrated in Fig. 2, which shows the electrogram record.

The electrogram in $\frac{1}{4}$ K solution is shown after stimulation in (c) and on addition of acetylcholine in (d). Stimulation in the presence of acetylcholine then caused fibrillation as in (e), continuing six minutes later as in (f). When the acetylcholine was removed by changing the bath fluid a normal rhythm returned as in (g).

Once the procedure which has been described was followed, flutter or

FIG. 2.—(c) E.C.G. in $\frac{1}{4}$ K solution after stimulation; (d) beats arrested by addition of acetylcholine; (e) fibrillation one minute after stimulation in presence of acetylcholine; (f) six minutes later; (g) after washing out acetylcholine.