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Gastric secretion in myxœdema. By F. LEE-LANDER.

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Previous observers, on the relationship between myxœdema and changes in gastric secretion, have held divided opinions on the subject. The majority [Sturgis, 1922; Lockwood, 1925; Lerman and Means, 1932; Berryhill and Williams, 1932] favour the view that gastric secretion is depressed and that there is an increase in the incidence of achlorhydria. Their views are based on a very small number of cases, and no attempt is made to follow the gastric secretion after the myxœdematous changes have been controlled. One observer [Levy, 1929] favours the view that myxœdema is associated with hyperchlorhydria, and reports a depression in the level of the secretion following thyroid medication.

The present series of twenty cases of myxœdema consist of twelve cases in which histamine test meals were performed before thyroid medication was given and eight cases which had been under treatment for several years before being examined. These eight cases were, to all intents and purposes, normal persons, and their gastric functions were investigated in order to see whether any showed achlorhydria, and secondly, to form a small series of controls to the ten untreated cases of myxœdema. Of the twelve untreated cases, six may be classed as severe cases of myxœdema, and six as slight cases. All had histamine test meals performed as soon as the diagnosis was made, and in eight cases the investigation was repeated (in three cases on several occasions) between 9 months and 1 year after the institution of therapy. Two of the severe cases of myxœdema showed achlorhydria. Although there are differences to be noted in the test meals before and after cure, these differences are not uniform; in some cases there is an increase in HCl secretion and in some a decrease. Further, in the two cases of achlorhydria this condition has persisted.

One case is worthy of note, as test meals were performed whilst myxœdema was developing. It was noted in this patient that following

thyroidectomy a low B.M.R. reading was obtained, although no symptoms were present and the patient's appearance was normal except for exophthalmos. During the course of the next year the patient began to complain of shortness of breath, lack of sweating, poor memory and hair falling out, and she gradually assumed a myxœdematous appearance. Thyroid medication was withheld during that year, as it was hoped that spontaneous cure from hypertrophy of the remaining thyroid tissue would occur. During this year three histamine test meals were performed. Six months after the institution of thyroid therapy a fourth test meal was performed, and all of these gave results within the limits of normal variation.

In another case, which showed a fall in HCl secretion following thyroid treatment, a further test meal was performed, and on this occasion a rise in secretion was recorded.

Of the eight treated cases, two exhibited achlorhydria and one a low secretion level (6 c.c. *N*/10 HCl). The two cases of achlorhydria and two further cases showing moderate HCl secretion were re-examined. The achlorhydria persisted in both cases, and one case with moderate secretion remained unaltered and in the other there was an increase in secretion.

In such a small series of cases as is contained in this investigation it is meaningless to draw conclusions from percentages and comparison with figures obtained from normals, and it is only by consideration of each individual case that any lesson may be learnt. The following conclusions are suggested:

(1) The achlorhydria which occurs in myxœdema is uninfluenced by thyroid medication.

(2) That there is no constant change in the gastric secretion either (a) whilst myxœdema is progressing, or (b) when myxœdema is cured.

(3) That the level of gastric secretion in myxœdema varies between complete achlorhydria and hypersecretion (96 c.c. *N*/10 HCl), which variation also occurs in a series of normal cases.

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Impedance angle determinations: various correlations and experiments. By J. D. ROBERTSON and A. T. WILSON. (*From the Courtauld Institute of Biochemistry and the Department of Physiology, Middlesex Hospital, W. 1.*)

1. Using the Brazier Bridge [Brazier, 1933] impedance angle (I.A.) determinations, with certain other measurements, were made on 120 members of the nursing staff of Middlesex Hospital and on certain numbers of unselected patients.

In the normal female group, plotting of I.A. values against (i) height, (ii) weight, (iii) surface, showed no obvious correlations.

In the case of forty-five patients, in addition to the correlations mentioned above, forearm circumference showed no relation to I.A. values, although the usual sex difference was, of course, obvious. In 104 patients in the medical and surgical wards of Middlesex Hospital no obvious correlation was found with any of the commoner disorders except Grave's Disease and myxœdema (as previously described and confirmed [Brazier, 1933; Robertson and Wilson, 1934]). A single case of typical Addison's Disease, a middle-aged female on satisfactory treatment with cortical extract, was examined by the courtesy of Dr Levy Simpson. She gave the low I.A. reading of 0.088 (23 on the clinical scale devised by Brazier).

Two cases of myxœdema on treatment with thyroid extract showed a significant downward movement of I.A. values; and three cases of partially thyroidectomized Grave's Disease, beginning some three weeks after operation, showed a marked upward movement of I.A. to nearer the normal mean. These results confirm those reported by Brazier.

2. Single and series determinations of two male subjects were made using two arm baths for determinations on one individual, and three arm baths, one common to an arm of each subject, for series determinations.

	I.A.	R
Subject (i)	0.110	212
„ (ii)	0.144	179
(i) and (ii) series	0.130	361
Subject (iii)	0.107	218
„ (iv)	0.139	209
(iii) and (iv) series	0.130	392

The I.A. value approximates to the mean of two readings, the resistance (*R*) to the sum.

3. Five student volunteers, after determinations of I.A., and resistance values, each drank 1 litre of saline. Ten and thirty minutes later there was no significant change in these readings.

4. The I.A. of six decerebrate cats was measured between fore and hind paws, each pair immersed in an earthenware vessel containing 1 litre of normal saline. When killed by rebreathing chloroform, they showed no change of I.A. and *R* values before and after cessation of detectible heart beat. After four hours the I.A. values had risen by an average of 11 p.c., resistance by 9 p.c. In twelve hours the figures were 33 p.c. average increase of I.A. and 42 p.c. of resistance.

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Estimation of the arm to tongue circulation time by means of decholin and comparison with the basal metabolic rate. By M. KREMER and J. D. ROBERTSON. (*Middlesex Hospital.*)

Decholin is the sodium salt of dehydrocholic acid, and it was first employed for determining the circulation time by Winternitz. It is injected into a vein in the ante-cubital fossa and gives an intensely bitter taste and smell on reaching the mouth and pharynx. If the determination is performed correctly the end point is extremely sharp and can be readily detected by the subject.

To obtain the sharpest end point it is necessary to wait 30 sec. after inserting the needle into the vein in case any drops of the solution have been carried in, and then to inject 5 c.c. of a 20 p.c. solution of decholin as rapidly as possible. If a number 12 needle is used this takes from 3 to 4 sec. An assistant measures with a stop-watch the time from the beginning of the injection until the subject appreciates the bitter taste.

Decholin is non-toxic and the taste lasts for 15–20 sec. only. There are no contra-indications to its use, and determinations can be made several times in succession. The histamine method (Bain) does not possess these advantages. If the pulse rate is under 40 per min. the decholin diffuses in the blood stream and the end point is so indefinite that it cannot be determined.

In order to have comparable results all the measurements reported here were made under basal conditions and usually just after the basal metabolic rate had been estimated. As with the B.M.R. technique, circulation times were estimated on two successive days and the second result taken as the basal circulation time.

In normal medical students a correlation of the order of 0.9 was found between the B.M.R. and the circulation time on the assumption that the B.M.R. determination is accurate to ± 2 . As can be seen from Table I in

TABLE I.

Student's No.	1	2	3	4	5	6	7	8	9	10	11
B.M.R.	-11	-6	+1	+9	+9	-6	-11	-1	+2	+19	-2
Circulation time in sec.	17.6	17.4	15	13	13	18	15.4	16.8	13	13	15.2
Student's No.	12	13	14	15	16	17	18	19	20	21	
B.M.R.	0	-7	-13	+5	-8	-14	+5	0	+1	-6	
Circulation time in sec.	15	18	18.4	17	19	19	14	17.4	15.2	19	

no case of a subject with a B.M.R. that was normal or less than normal was the circulation time less than 14 sec. The range was 14-19 sec.

A series of observations were made on patients with thyrotoxicosis and it was found that though a raised B.M.R. gave a shortened circulation time, it was impossible to predict the degree of rise of B.M.R. from the circulation time.

TABLE II.

Case No.	1	2	3	4	5	6	7
B.M.R.	+46	+48	+45	+80	+52	+46	+48
Circulation time in sec.	12	9.4	11.5	9.4	10	11.8	10

If the B.M.R. was lowered (by the administration of iodine or thyroductomy in thyrotoxic patients or the stopping of thyroid in myxoedema) the circulation time was increased. If the B.M.R. was raised (giving thyroid to a hypothyroid patient) the circulation time was shortened.

TABLE III.

Case No.	1†	2§	3*	4*	5*	6†	7*	8†	9†
Initial B.M.R.	+28	-20	+58	+42	+13	+22	+39	+69	+12
Initial circulation time in sec.	12.2	17.6	11.2	12	13.8	9.4	10.8	9.5	11.2
Final B.M.R. after treatment	-28	-11	+12	+17	-5	-9	+20	+24	-9
Final circulation time in sec.	20	16	13.5	13	16	14	12.6	12.5	15.5

* Iodine. † Thyroductomy. ‡ Stopping thyroid. § Giving thyroid.

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Rickets on a diet with adequate cod-liver oil, and scurvy on a diet containing adequate orange juice. By ALAN MONCRIEFF. (*Middlesex Hospital.*)

Two children recently under my care at the Hospital for Sick Children, Great Ormond Street, illustrate difficulties in the simple etiology assumed for the deficiency diseases.

1. Female child of 17 months had been artificially fed from birth on a rational diet. Until March 1935 the child received in addition 1 drachm daily of a good cod-liver oil, then a preparation containing cod-liver oil and Parish's food in equal parts, of which half an ounce had been given daily. From June until the time of admission she had received another preparation reputed to be 25 times as rich as cod-liver oil in vitamin D, and of this she had had 90 minims daily. Admission to hospital was sought for a "fit" and general irritability dating from bronchitis in March 1935. Clinically the child presented all the signs of rickets, and there was also evidence of tetany in the form of facial irritability and laryngismus stridulus. Her serum calcium was 4.3 mg. per 100 c.c. (ionic calcium 1.9 mg.) and the inorganic blood phosphorus 3.2 mg. per 100 c.c. X-ray examinations showed florid rickets. There is no evidence of renal disease nor of coeliac disease. Improvement has been slow with adequate vitamin D intake and calcium intravenously.

2. Male child aged 10 months had been breast fed for some weeks and then changed on to a boiled milk and water mixture with some attempt at mixed feeding for a few weeks. He had been given orange juice daily ever since birth, amounting to about half an orange daily for many months. He had been perfectly well in every way until 3 days before admission, when he appeared to have pain in his legs. On admission he had the classical tenderness in the legs of scurvy, typical changes in the gums round two erupted teeth, hæmaturia (microscopic) and X-ray changes at the ends of most of the long bones. In view of the apparent non-absorption of vitamin C he was given 400 mg. of ascorbic acid intravenously. By next day the child was less miserable, and within 48 hours there was obviously less tenderness. Four days after admission the child would laugh on being touched over the limbs, the gums were improving and the urine was free from blood. The child has now been accustomed to a good mixed diet with fruit juice daily, and the X-rays show definite healing changes.

Electrical phenomena recorded from the skin. By W. F. FLOYD
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It is the claim of many investigators that two distinct phenomena of an electrical nature may be recorded from the skin of the human subject in response to certain stimuli. The one is the Féré phenomenon [Féré, 1888] and termed the "psycho-galvanic reflex" by Veraguth [1909]: the other is the Tarchanow phenomenon [Tarchanow, 1890].

The Féré phenomenon is the increase in the current flowing through the body from an external circuit incorporating a source of current, consequent upon suitable stimulation of the subject. The Tarchanow phenomenon is the complex change in the current flowing through the body, following stimulation, when there is no source of current in the external circuit. The source of the current in the latter case is believed by most investigators to be the differences in potential between different parts of the skin, and the response is attributed to changes in these potentials.

In all the circuits employed for the investigation of the two phenomena, the current variation has been detected by the change in the deflection of a galvanometer connected in the external circuit. In the case of the Féré phenomenon the response of the subject has been expressed, usually by the change in the "apparent resistance" of the body, and in the case of the Tarchanow phenomenon by the potentials which, connected in place of the subject, produce the same galvanometer deflections.

Very few precautions have been taken in the past to ensure constancy of the conditions of measurement, and, in particular, the initial current through the subject has been different in nearly every case; only Prideaux [1921], Davis [1929] and Darrow [1932] have described circuits, for the measurement of the Féré phenomenon, in which the current for each subject may be brought to the same initial value. During the reaction the current through the subject has always varied—in fact this is the phenomenon.

In the author's investigations of the E.M.F.'s from the skin, the current through the subject is maintained at a constant value for the duration of each experiment. That is to say, the current does not vary during the subject's reaction to stimulation, as it does in all the circuits used by investigators of the Féré and Tarchanow phenomena. The response measured in these experiments is the decrease in the E.M.F. pro-

duced by the body, following stimulation. The current is maintained constant by the use of a thermionic valve circuit, and the E.M.F. is measured with the aid of a battery-coupled valve amplifier [Floyd, 1935]. The E.M.F. changes observed in this case constitute a phenomenon distinct from that of Féré or Tarchanow, but the physiological basis is probably the same.

With no current flowing through the subject, potentials and potential changes are recorded. These potentials are the true potentials from the skin and the inter-electrode tissues, and are not influenced by current flow as occurs in the case of the Tarchanow phenomenon. Except for the interference with the subject arising from the electrodes, which are in contact with the skin, the potential changes, recorded in this way, are probably more nearly representative of the natural activity of the subject than are any other electrical measures employed up to the present time.

The records of E.M.F. and potential obtained from the skin in the manner described here, in response to suitable stimulation of the subject, are similar in general nature to records of the Féré and Tarchanow phenomena: there are certain differences to be noted also. More detailed communications will deal with the physical and physiological factors concerned in these responses.

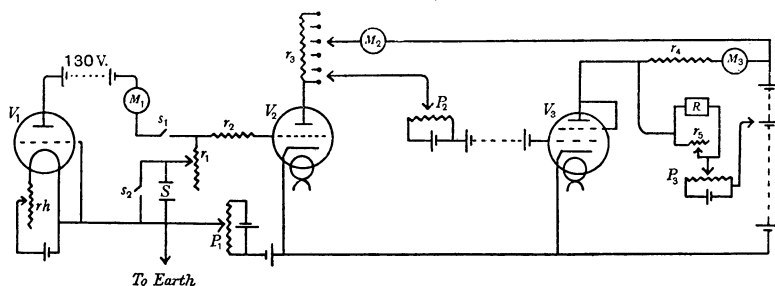
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Apparatus for the continuous recording of potentials and E.M.F.'s from the skin. By W. F. FLOYD (*Leon Fellow of the University of London*). (*Research Department, Institute of Education and Department of Physiology, Middlesex Hospital.*)

The apparatus described in this communication is designed for the measurement and recording of certain of the electrical phenomena observed in an external circuit when electrodes are connected to the skin of the human subject. It comprises a source of constant current and a two-stage amplifier, the output circuit of which incorporates a recording milliammeter. The subject is connected at *S*.

V_1 is a triode valve (Marconi R5V), operated at a low filament temperature, controlled by the rheostat rh , and at an anode potential of about 130 volts. Under these conditions the anode current indicated by M_1 is the saturation current, which measurements have shown to be constant to well within 0.01 p.c. of its value for changes in the anode potential of 1 volt, and constant to within 0.001 p.c. of its value for changes of 100 mV. Constant current values of from 1 to 100 μ A., to which these figures apply, are obtainable by adjustment of rh , and the saturation current remains constant for several hours. The constant current flows through the subject who is included in the anode circuit of this valve.



The equivalent potential changes introduced into the anode circuit of V_1 , by appropriate stimulation of S , are considerably less than 1 volt and frequently less than 100 mV. The current through S may be considered constant, therefore, to within less than 0.01 p.c. at most during all experiments in which the E.M.F. from the skin is measured.

V_2 and V_3 , together with the associated circuits and equipment, comprise the two-stage amplifier and the recorder. The resistance shown at r_1 is built up of a number of decade resistance units of maximum resistance of 211,000 ohms; that at r_2 has a value of 0.25 megohm. The valve V_2 is operated as a voltage amplifier and is a Mullard 994V with a rated amplification factor of 125. The overall amplification obtained from this stage may be varied by adjustment of the connections to the tapped, wire-wound resistance r_3 . The output valve V_3 is chosen for its large (anode current, grid voltage) conductance value (12 mA./V.) because the amplifier is required to have a large overall transconductance, and not necessarily a large amplification factor, in order to operate the recorder. The Marconi N41 pentode valve can be used in this position.

The recording milliammeter is an Evershed and Vignoles instrument with a range of 0-3 mA. It is connected in a network which is adjusted, by means of the tapping on the H.T. battery, so that the current is zero

or almost zero in the arm of network in which the recorder is located. In this way the normal steady anode current of 15 mA. is compensated for, and only changes in the anode current influence the recorder. The resistance at r_4 has a value of 3000 ohms, and r_5 is a shunt by which the sensitivity of the recorder may be reduced. The recorder has a natural period which is not greater than 0.25 sec. and it is well suited, therefore, for the investigation of the slowly changing electrical phenomena which may be recorded from the skin.

The E.M.F. measurements, with constant current flow through S , are made with the switch s_1 closed and with s_2 open: with both open, the apparatus is adjusted for the investigation of skin potentials. The amplifier is calibrated by closing both switches and passing the constant current through a known value of resistance at r_1 . In this way the recorder scale may be calibrated directly, in terms of millivolts applied to the grid circuit of V_2 .

By means of three potentiometers, P_1 , P_2 , P_3 , the amplifier may be accurately balanced, P_1 and P_2 controlling the grid circuits of the amplifier and P_3 controlling the zero of the recorder without disturbance of the amplifier balance. The total resistance of P_3 had to be small so that the resistance of the compensating network should remain as nearly constant as possible for different settings, and the value chosen is 100 ohms. The maximum circuit resistance due to P_3 is, therefore, .25 ohms. Coarse adjustment of the zero of the recorder is carried out mechanically and fine adjustment by P_3 can be effected without decreasing the net circuit resistance of P_3 below 20 ohms. The error introduced thereby is less than 1 p.c. of the instantaneous scale reading of the recorder.

Observations on the renal circulation in non-anæsthetized dogs.

By H. HANDOVSKY and ADLI SAMAAAN. (*From J. F. Heymans' Institute of Pharmacology, University of Ghent.*)

Janssen and Rein [1928], working on decerebrate dogs, noted that the renal blood flow was not altered during the course of water diuresis nor after the administration of the actively anti-diuretic post-pituitary extract; they concluded that no direct relation existed between the renal blood flow and the urinary secretion.

In the present research continuous observations, lasting 6–10 hours, were made on thirteen conscious dogs on (1) the blood flow in the renal artery (thermo-stromuhr of Rein [1928]), (2) the blood-pressure (cannulated brachial or carotid artery [Samaan, 1935 a]) and (3) the urinary flow (cannulated ureter).

Water diuresis. Tap water—whether taken voluntarily, given by stomach tube or by slow intravenous infusion—was followed by the typical water diuresis curve [Klisiecki, Pickford, Rothschild and Verney, 1933]. The renal blood flow presented a progressive increase which preceded that of the urine flow; in three cases, however, diuresis did not take place and the blood flow was hardly altered. The blood-pressure showed no change or only a slight rise.

Splanchnotomy. Homolateral section of the major and minor splanchnic nerves in the conscious dog was performed under local novocaine anaesthesia. Although the blood-pressure was only slightly disturbed, the blood flow as well as the urinary secretion were increased. An immediate temporary diminution of the blood flow was not uncommon.

Carotid sinus reflexes. Occluding the common carotid arteries was followed, as is well known, by a marked rise of the blood-pressure. The renal blood flow, however, presented individual variations; thus in some dogs a slight or a moderate increase took place, while in others a definite reduction was observed. Similarly the secretion of urine increased markedly except in the latter cases. After release of the carotid arteries the blood flow usually returned to its resting level, and not uncommonly it underwent occasional variations for a few minutes.

Post-pituitary extracts. Infundin (Burroughs, Wellcome and Co.), Pituglandol (Roche) and Posthypophyne (Palfijn) were employed. The intravenous injection of any of these extracts was followed by a definite diminution of the blood and urine flows; these effects were dependent on the doses given [Samaan, 1935 *b*]. It was invariably noted, firstly, that the blood flow recovered to its resting level much earlier than the return of the urine secretion to the normal value and, secondly, that the effect of post-pituitary extract on the blood flow became more pronounced after establishing water diuresis. The blood-pressure showed a slight rise.

Adrenaline. The intravenous injection of small doses (0.00002–0.0005 mg. per kg.) was followed by a definite reduction of the renal blood flow and a transient negligible inhibition of urine; the blood-pressure showed a moderate rise which soon passed away. Larger doses, although associated with similar but more marked changes in the urine flow and in the blood-pressure, affected the renal blood flow in a peculiar way, namely, (*a*) an immediate temporary reduction followed by (*b*) a pronounced increase which coincided with the adrenaline hypertension, then (*c*) a diminution—sometimes very marked—and finally (*d*) a return to the resting value. As in the case of post-pituitary extracts the effect of

adrenaline on the renal blood flow became so pronounced after establishing water diuresis that even 0.0004 mg. per kg. affected the blood flow in the same manner as the large doses did.

Observations on the effects of tissue dehydration and diuretics are devoted to a further communication.

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Actions of antidromic impulses on ganglion cells.

By J. C. ECCLES. (*Physiological Laboratory, Oxford.*)

Volleys of impulses travelling antidromically down the main postganglionic trunk of the superior cervical ganglion have been set up by stimuli applied through electrodes on the isolated trunk several mm. beyond the ganglion. When the grid lead to the amplifier is placed on the ganglion, and the earthed lead on the postganglionic trunk between the stimulating electrodes and the ganglion, the passage of an antidromic volley is signalled by the usual diphasic action potential. With strong stimuli this diphasic response is double, the first part being due to the fast impulses, S_1 , in the fibres supplying the structures in the orbit, the second part to the slower impulses, S_2 , in the vasomotor and pilomotor fibres.

An antidromic volley renders the S_2 ganglion cells absolutely refractory, a maximal preganglionic volley failing to set up a discharge for at least 5 msec. Recovery occurs gradually during a relatively refractory period in which a preganglionic volley sets up a smaller discharge with a longer synaptic delay, the lengthening never being more than 3 msec. The latter part of the relative refractoriness runs on to the phase of depressed excitability described later.

The diphasic response to an antidromic volley overlaps a later slow positive potential wave (ganglion positive to postganglionic trunk), which closely resembles the wave set up in the ganglion by a preganglionic volley, but it runs a slightly quicker temporal course (maximum at about 80 msec.) and has always been smaller in potential, though in some experiments this discrepancy has been very slight. Various methods of analysis, e.g. the action of nicotine, have shown that the slow potential

wave set up by a preganglionic volley is composed of a negative wave, *N*, overlapping a slower positive wave, *P*, both waves reaching a maximum at about 20 msec., but *N* decaying at more than twice the rate of *P*. Similarly analysis shows that the slow potential wave set up by an antidromic volley is composed of an *N* wave overlapping a *P* wave, but, relative to the *P* wave, the antidromic *N* wave is always smaller.

The *N* wave set up by a preganglionic volley is closely associated with an increased excitability of the ganglion cells, c.e.s., and similarly with the *P* wave and a diminished excitability or c.i.s. This close association also obtains for the *N* and *P* waves set up by an antidromic volley, the relatively smaller *N* wave being associated with a small excitation that is submerged beneath the depression of excitability associated with the larger *P* wave, and only produces a demonstrable facilitation when this *P* wave and its associated depression is occluded by a pre-existent *P* wave. Analysis by the interaction of successive volleys and by the action of nicotine indicates that this excitation and depression produced by a preganglionic volley are identical with the c.e.s. and c.i.s. set up by a preganglionic volley.

It has been suggested that the slow negative and positive potentials of nerve cells and the associated excitation and inhibition are analogous to the negative and positive after-potentials of nerve and the associated supernormal and subnormal phases, and are only set up in consequence of the discharge of impulses by those cells. However, the c.e.s. responsible for the facilitation of the ganglion cells in the subliminal fringe cannot be thus explained, and corresponding to this there is evidence that a subliminal preganglionic volley sets up a small *N* wave. Moreover, even when the refractory period set up by an antidromic volley prevents a preganglionic volley from evoking a discharge of impulses from the ganglion cells, the *N* wave and c.e.s. of the latter volley are not appreciably diminished. Thus preganglionic impulses must be able to set up in the ganglion cells c.e.s. and the associated *N* wave independently of the discharge of impulses by those cells. That this is so is also indicated by the much smaller *N* wave set up by an antidromic volley, for presumably as in peripheral nerve after-potentials would be independent of the direction of travel of the impulses, an antidromic impulse producing the same effect as the discharge of an impulse.

With the *P* wave and c.i.s. the evidence is less clear, but, as in many experiments the *P* wave produced by a maximal antidromic volley is much less than that set up by a maximal preganglionic volley, it seems that preganglionic impulses must also give rise to a *P* wave additional to that set up by the discharge of impulses by ganglion cells, such preganglionic impulses being inhibitory.

Thus we have preganglionic impulses setting up an N and probably a P wave by direct action on the ganglion cells as well as indirectly through the impulses which they stimulate the ganglion cells to discharge, and both N waves are associated with an increased excitability and both P waves with an inhibition. It seems probable that the preganglionic and antidromic impulses cause the ganglion cells to produce N and P waves by acting on them in some identical way. The only likely factor which would be common to both seems to be the eddy currents associated with the transmission of these impulses. It is conceivable that such currents in preganglionic fibres lying in close contact with dendrites would have an action on the ganglion cells very similar to impulses in the dendrites themselves.

A new type of interaction experiment with the retinal action potential. By RAGNAR GRANIT, B. RUBINSTEIN and P. O. THERMAN. (*Physiology Institute, Helsingfors University.*)

The evidence for interaction between adjacent areas in the retina, inasmuch as it refers to the retinal action potential, has recently been criticized by Fry and Bartley [1935] on the basis of an experiment which they hold to demonstrate that the main part of the initial positive b -wave is caused by non-focal irradiated light. In this experiment (rabbit's eye) two adjacent bright areas against a black background were stimulated alternately so that one area was covered the moment the other one was exposed. Separately stimulated, the areas gave potentials a and b . At fast rates of alternation summed responses, $a + b$, of partly overlapping sequence were expected, but contrary to expectation no potential whatsoever was obtained (presumably after the first initial b -wave caused by the first flash). The absence of an effect was explained by the hypothesis, that the sum total of stray light, being independent of which area was stimulated, acted as a constant stimulus of far greater strength than the alternating focal points. The focal light, on this hypothesis, elicits only a negligible fraction of the b -wave. The rest is due to the receptors in the non-focal area.

In view of work which for some time has been going on in this laboratory the "stray light" hypothesis seemed to us extremely improbable. We therefore decided to test it by removing irradiation as a factor in the experiment and by simplifying the experimental conditions in general.

From a dark-adapted, excised and enucleated frog's eye leads were taken to a five-stage condenser coupled amplifier (large condensers)

operating a cathode-ray oscillograph. With a lens of good optical properties, possessing a closely fitting iris diaphragm, the images of two bright spots of light against a black background were focused directly on to the retina. At their focus the spots were about 0.4 mm. in diameter and about 0.3 mm. apart. The focusing (micrometer screws) having been carried out, we first reduced the opening of the diaphragm and then diminished the intensity of the light by means of neutral tint filters until the potentials (*b*-waves), elicited by the single spots, were about $50\mu V$. With the full intensity and the diaphragm maximally opened a common faint halo of irradiated light could just be seen around the spots when the retina was replaced by a strip of white paper. About $50\mu V$. were obtained with the diaphragm narrowed so that the spots themselves could just be detected on the retina, the intensity afterwards having been reduced to 1/100th of the original level.

If the *b*-waves of the individual spots, *A* and *B*, separately stimulated, be *a* and *b*, a large deficit in the sum, *a* + *b*, with simultaneous stimulation, might be due to interaction, irradiation or other factors. Such cases have occurred, but they need not detain us here. Our criterion of restricted stimulation was, that, within 10–15 p.c. the sum, *a* + *b*, should be obtained when both were stimulated simultaneously, an interval of 3 min. between the exposures being allowed for restitution. As the non-focal halos of the individual stimuli overlapped over an area of several mm. in diameter and probably were subthreshold stimuli anyhow, a sum total of approximately *a* + *b* must mean that the individual focal effects were responsible for the potentials obtained, or at least for some 85–90 p.c. of them, and hence that non-focal irradiated light was negligible.

Absence of irradiation having been established by this criterion *in casu*, *B* was made to follow *A* after a short interval of darkness. Despite the fact that the two stimuli summed when simultaneously exposed, the second, *B*, gave no effect whatsoever when it followed after the first, *A*—roughly on top of the *b*-wave elicited by *A*. Thus, although the retinal locus of *B* itself had not been stimulated, it responded as if the flash on *A* had spread to it. In fact, the same result would have been obtained by stimulating *A* twice at the corresponding interval. We conclude that the electrical charge, caused by restricted focal stimulation, spreads over adjacent parts of the retina, thereby indirectly causing changes which cannot be distinguished from those that follow from direct stimulation.

The results disprove Fry and Bartley's hypothesis that the retinal

action potential is caused by stray light, provide a simple explanation of their results in terms of interaction, and confirm the view [Granit, 1933; Granit and Therman, 1935] that the retinal action potential is localized to the synaptic layers of the eye.

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Distribution of histamine between plasma and red blood corpuscles. By G. V. ANREF and G. S. BARSOUM. (*University of Cairo Medical Faculty, Egypt.*)

It has been shown by Barsoum and Gaddum for the rabbit that about 15 p.c. of the histamine content of 1 c.c. of blood is in the plasma and about 85 p.c. in the red blood corpuscles. Considering the volume of corpuscles as 40 p.c. this gives a corpuscle/plasma ratio of histamine as 10 : 1. In our experiments, in which we determined the histamine equivalent of whole blood and plasma as well as the hæmatocrite value, we found for the rabbit ratios well above 10 : 1, sometimes as high as 18 : 1. In dog's blood, however, this ratio is of the order of about 1 : 1. The present experiments were made on dog's blood which was defibrinated, citrated or to which chlorazol fast pink was added as an anticoagulant. When histamine is added to the blood the original 1 : 1 ratio is disturbed only for a very short time. Blood which is centrifuged immediately after addition of histamine may show a ratio of about 4 or 2 : 1, but when it is centrifuged about 5 min. later no difference between corpuscles and plasma can be found. This was found to hold true for concentrations varying between 20 and 15,000 γ per litre of blood. It is of interest that although histamine penetrates into the blood corpuscles with extreme ease it diffuses or becomes detached from them with the greatest difficulty if at all. A few minutes after the addition of histamine to the blood, the corpuscles are centrifuged, washed in normal plasma and suspended in the plasma of the same blood to which no histamine was added. The histamine-rich corpuscles in the histamine-poor plasma are then kept for different lengths of time at 37° C., centrifuged, and the histamine is determined in the plasma and in the whole blood, while the volume of the corpuscles is determined by the hæmatocrite. The following experiments serve as an example. The histamine

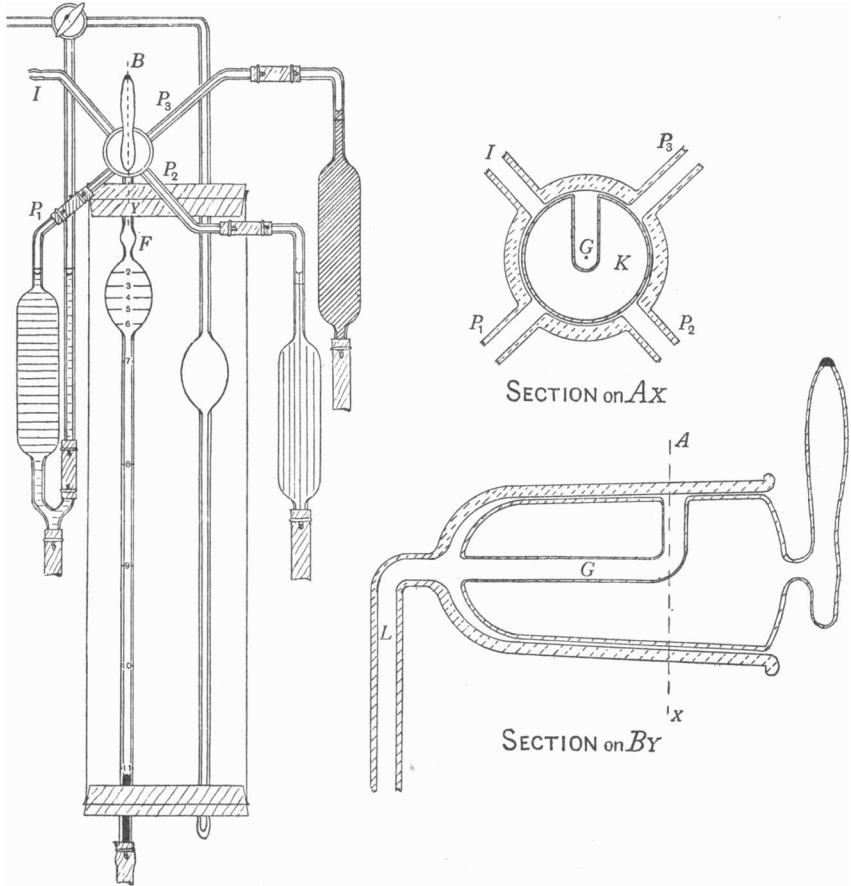
concentration is given in γ per litre. The determinations were carried out by the method of Barsoum and Gaddum [1935], the accuracy of which was confirmed by us to be somewhat under 10 p.c. Each determination was repeated three to four times. In Exp. 3 the red blood corpuscles were not washed in the histamine-poor plasma, hence the histamine content of the plasma after it had been changed became increased.

		Exp. 1	Exp. 2	Exp. 3
Before addition of histamine:	Whole blood	33	—	25
	Plasma	33	—	25
After addition of histamine:	Whole blood	500	500	15,000
	Plasma	500	500	15,000
		Red blood corpuscles washed, plasma changed	Plasma not changed	Red blood corpuscles not washed, plasma changed
Plasma after 20 min.		33	—	250
" 40 "		33	—	—
" 60 "		33	500	250
" 90 "		33	500	250
Whole blood after 90 min.		200	500	6,500
Corpuscles calculated from hæmatocrite value		500	500	14,000

In contrast to the behaviour of histamine in shed blood, it is well known that it disappears from the general circulation within a comparatively short time. We found in the dog that after an intravenous injection of 0.5 mg. per kg. body weight the histamine concentration of the blood returned to normal in about 3 hours. The cause of this rapid disappearance of histamine from the circulating blood lies mainly in the tissues and most probably in the presence of histaminase. This is supported by the fact that an addition of fresh extracts of tissues to the whole blood *in vitro* containing a high concentration of histamine leads to a rapid disappearance of it from the plasma as well as from the blood corpuscles. For example, the histamine concentration of the blood was increased to 500 γ per litre, and 1 hour later it was found to be the same. Neither did the histamine-rich blood corpuscles which were suspended in a plasma containing 25 γ per litre add any histamine to the plasma nor did they lose any histamine themselves. On addition to the histamine-rich corpuscles suspended in histamine-poor plasma of 0.25, 0.5 and 1 c.c. of a saline kidney extract to 10 c.c. of blood each, the corpuscular histamine diminished in 1 hour by 20, 35 and 45 p.c. respectively. The kidney extract added to the histamine-rich corpuscles which were suspended in histamine-rich plasma caused a diminution of histamine of about the same order.

A simplified arrangement for the Haldane gas-analysis apparatus. By DOUGLAS H. K. LEE. (Introduced by C. LOVATT EVANS.)

In this arrangement there is only one tap connecting the burette to the absorption pipettes, no matter how many of the latter there are.



The tap key (*K*) contains a single bore (*G*) commencing at its posterior end (section on *BY*), running forwards along the axis of the tap, then bending at right angles and emerging at the side in the plane of the gas intake (*I*) and pipette leads (section on *AX*, *P*₁, *P*₂, *P*₃), which are arranged in a circle at right angles to the tap axis. The burette lead (*L*) opens into the back of the tap opposite the key bore. The calibration of the burette includes the small space at the back of the tap and the bore of the key. A small splash bulb (*F*) above the main burette bulb is advantageous.

The advantages of this arrangement are: (i) simplicity of use and explanation to students, (ii) reduction of possibilities of tap leakage, (iii) impossibility of mixing the contents of absorption tubes or of getting the contents of more than one into the burette. The small unjacketed dead space at the back of the tap is not a disadvantage if balanced by a proportional unjacketed space in the control burette system.

Acknowledgments are due to Mr Trendall for interest in the production of this arrangement, and to the Medical Research Council for a grant from which expenses were defrayed.

The regulation of cardiac rate during exposure to heat.

By R. A. GREGORY and D. H. K. LEE.

That the cardiac rate of the intact subject rises during exposure to heat is common knowledge. Other circumstances also tend to raise the cardiac rate; and it is interesting to notice what happens when one of the latter factors is coincident with heat. Others [Dill *et al.* 1931; Hill and Campbell, 1922] have shown that moderate muscular work has a greater effect upon cardiac rate when the environment is hot. We have observed similar results when the incidence of dehydration, food intake, and atropine or thyroxine administration is added to that of exposure to a dry-bulb temperature of 110° F. with the wet-bulb 90° F.

Dehydration. After 5 hours in the hot room, subjects deprived of water had an unstable average rate of 122 beats/min., while others receiving water had a steady average rate of 91 beats/min. Dehydration, acting alone, would probably not produce such a difference [Keith, 1924].

Food intake. The consumption of two boiled eggs, four "cracker" biscuits and 1 oz. butter in the hot room raised the rate by 14 beats/min. At a normal temperature such a meal has little effect.

Atropine. In 2 hours the hot room raised the pulse rate of a subject by 8 beats/min. at the most; in a room at normal temperature 1/75 grain of atropine raised it by 8 beats/min.; the same dose in the hot room raised it by 39 beats/min.

Thyroxine. In 2 hours the pulse rate of a subject in the hot room was raised by 14 beats/min. when he was reacting to 8 mg. of thyroxine injected 4 days previously, as against the outside maximum of a rise of 8 beats/min. in the same room without thyroxine.

It is evident from these observations that when two factors are acting coincidentally upon the mechanism controlling cardiac rate, the resultant effect may be quite different from the algebraic sum of the effects of the same factors acting separately. It seems important that this fact should

be borne in mind when attempts are made to apply to an organism under natural conditions the results of experiments in which variables have been studied singly. It would be interesting to apply similar tests to other bodily equilibria.

We are indebted to the London School of Hygiene and Tropical Medicine for the use of the Air-Conditioning Room, to the Medical Research Council for a grant to one of us (D. H. K. L.), to Dr C. Reid for assistance in the hot room and to Prof. C. R. Harington for the supply of thyroxine.

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A modified balanced-input amplifier. By D. A. Ross.

In the balanced amplifier designed by Matthews [1934] the impedance to earth is the same for both input leads. The system is of value for multiple recording [Adrian and Matthews, 1934], and is, in addition, insensitive to stray electrostatic fluctuations in the neighbourhood of the preparation; but it tends to be somewhat less quiet

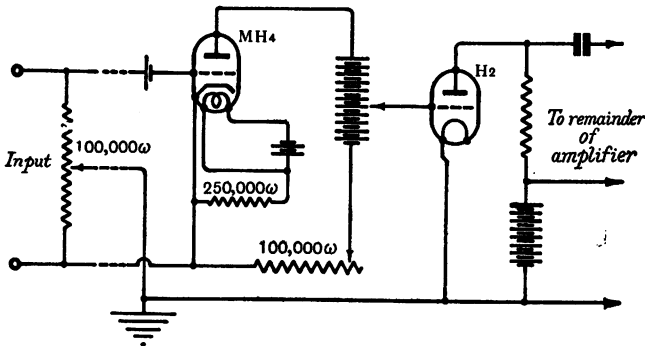


Fig. 1.

than the usual grid-earth-input amplifier because the grid-cathode impedance of both valves remains high whether the preparation is connected across the input or not. It accordingly seemed advisable to search for a circuit using the ordinary grid-cathode input, but in which the impedances to earth of both input leads could still be balanced if desired.

Fig. 1 shows such a circuit. The input valve is battery-coupled to the second stage, whose input is of the usual grid-earth type. The grid resistor of the first valve is a 100,000-ohm potentiometer, the movable

contact of which is earthed.¹ This enables one to "tune out" electrical interference which may cross the input leads asymmetrically, and also permits ready conversion of the amplifier into the grid-earth type if required.

It will be noted that the presence of any leak between the second-stage grid line and earth will cause a partial feed-back, more than 90° out of phase with the input potential, on to the first grid, thus causing a loss in sensitivity. The grid-filament capacity of the second valve, together with the capacity to earth of the H.T. battery, provide such a leak for high frequencies, so that the amplification falls off as the frequency rises. The system is therefore best suited to low-frequency

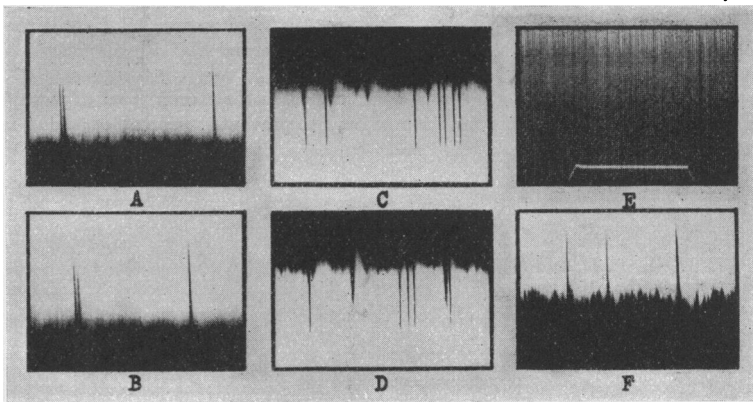


Fig. 2. For explanation see text.

amplification; but experiment shows that it will handle the usual run of nerve-action potentials tolerably well. Fig. 2 A and B show corresponding records of action potentials from a frog's dorsal cutaneous preparation, A taken with the input potentiometer turned down to the cathode end, and B with it approximately in the central position. The balancing causes practically no reduction in the recorded height of the impulses, while the base line remains as good as before.

The circuit may also be used with the first stage capacity coupled to the second, provided that the grid resistance for the second valve is very high. In this case, however, adverse feed-back is present at all frequencies, so that a considerable loss in amplification, greater at high frequencies, is encountered. Fig. 2 C and D are records containing both

¹ Direct connection between the cathode and heater circuit of the first valve is avoided because it would introduce the capacity to earth of the L.T. accumulator on to the lower input line. The system is not appreciably noisier than it is without the 250,000 resistance.

slow and fast impulses, taken with this last circuit from an antidromic dorsal cutaneous preparation. In C the cathode is earthed, as in A, while in D the input is approximately balanced and the oscillograph operated at four times the previous sensitivity in order to compensate for the loss in amplification. It is clear that in spite of its drawbacks the circuit could still be used for pure presence-or-absence work.

Fig. 2 E and F illustrate the ability of the amplifier (as in Fig. 1) to tune out interference. E shows the base line with earthed input, where the preparation is in place and a disturbance is being picked up from a neighbouring D.C. power line. In F the amplifier is working under exactly the same electrical conditions, except that the interference has been tuned out.

Note. With an unearthed system of this kind it is essential that all components of the first stage (and more especially the H.T. battery) should be very carefully insulated from earth. It is advisable to stand the first stage, batteries and all, on a sheet of clean glass, and to take whatever precautions may be necessary to prevent the spread of acid or fumes from the L.T. battery.

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