Brain Modelling

(A Brief Description of a Method of Studying the Anatomy of the Brain Based upon Reconstruction with Modelling Clay)

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It was my privilege to attend a course in brain modelling which was given recently at the Montreal Neurological Institute under the direction of Dr. Francis McNaughton, Assistant Professor of Neurology, McGill University. This particular method of learning neuroanatomy is not new but it may be unfamiliar to many of the readers of this Journal. I feel that the undergraduate readers of the Journal in particular should know that such a technique exists in order that they may be more likely to take advantage of the method if their postgraduate program carries them to a medical center where a course in brain modelling is offered. This article will also serve as advance notice that it is the intention of the Department of Anatomy of the University of Western Ontario to introduce an advanced course in neuroanatomy, based on the modelling method, as soon as space requirements can be met. This course will be a requirement for Fellows in the neurological sciences in the Graduate School and may be offered as an elective to a small group of highly selected undergraduates.

The general principles underlying the modelling method of learning neuroanatomy are as follows. By means of modelling clay a reasonably accurate reproduction of the main nuclei and fiber tracts of the central nervous system is built up on a scale four times that of the adult human brain. The information required for preparation of the model is obtained from the examination of gross sections through the brain in various planes and from a study of Weigert stained sections of the brain stem. Reference to texts and atlases is helpful, but is subordinated to the examination of original material. The mechanical act of moulding the clay to the proper size and shape and placing the structures in their correct anatomical position with respect to neighbouring nuclei and fiber tracts serves to fix the anatomical facts firmly in the mind. The
method is also important in helping to create a three dimensional mental picture of the brain, which is the aim of every teacher and student regardless of the method of instruction which may be used. To quote Dr. McNaughton, "Brain modelling is like a Methodist conversion — you are never quite the same afterwards." Although familiar only with the neurological component of this analogy I can heartily endorse the thought which Dr. McNaughton meant to express.

HISTORICAL DEVELOPMENT OF BRAIN MODELLING

Modelling anatomical structures as an aid in teaching and studying anatomy is no doubt as old as the science of anatomy itself. There is every possibility that brain structures have been reconstructed three dimensionally by many workers in many countries. Dr. Adolph Meyer was the first to make systematic use of the brain model preparation as a basis for courses in neuroanatomy. Dr. Meyer began to develop his ideas for teaching neuroanatomy by the reconstruction method while teaching at the University of Chicago in the last decade of the 19th century. He used the reconstruction method later, while teaching physicians in the State Hospital Service at the New York Institute. The modelling method achieved a still more definite form at the Johns Hopkins Medical School where Dr. Meyer had the collaboration of Dr. L. Hausman. An elective course which occupied two half days a week for one trimester was offered by these teachers. The method is used as the basis for an elective course in neuroanatomy at Cornell Medical School under Dr. Hausman and at Yale University. It may be in use in other medical schools of the United States unknown to the writer. In Canada, a course in advanced neuroanatomy based on the modelling method is offered annually at McGill University. This course was started by Dr. Francis McNaughton and Dr. John Kershman in the academic year 1937-38. The class is limited to ten students of whom the majority are Fellows in Neurosurgery or Clinical Neurology at the Montreal Neurological Institute.

All of the teachers referred to have stressed the importance of referring to actual preparations for the information necessary to reconstruct the nuclei and fiber tracts of the brain. The following quotation from the 1922 article by Dr. Meyer and Dr. Hausman illustrates the spirit of the course. "Facts and functions must be the issue of the course, not words. Books and written instructions are avoided. Actual material of embryology and comparative neurology furnish all the schemata that are needed; all other schemata are taboo."

MATERIALS REQUIRED

Abundant gross specimens of the brain are very helpful. Slices approximately one-half inch in thickness through the entire brain in
coronal and sagittal planes are particularly useful. A fairly close series of brain stem sections stained by the Weigert method is necessary for the reconstruction of its nuclei and fiber tracts. Since the reconstruction is made on a scale four times the size of the original sections, a series of photographs of the Weigert stained sections enlarged to four times the size of the original is valuable for making the measurements on which the reconstruction is based. A supplementary series of sections stained by the Nissl method serves to give more detailed information regarding the nuclear masses. A good reference library of neuroanatomical texts and atlases should be available even though original material forms the main source of data. The excellent drawings in depth contained in Krieg's Functional Neuroanatomy are particularly useful in helping to build up a three dimensional concept of the anatomy of the brain.

The wooden framework for the model can be turned out in any carpenter shop. The reconstruction is made in modelling clay which should be obtained in as many colours as possible. Nerves and certain tracts may be represented conveniently by coloured wire such as is used in radio work.

**OUTLINE OF THE METHOD OF RECONSTRUCTION**

It is not the purpose of this article to discuss the method of reconstruction in detail. The successive steps which are taken in the preparation of the model will be described in broad outline. The description which follows is based on the order of reconstruction now in use at the Montreal Neurological Institute.

As far as possible the various sensory and motor systems are distinguished by colour as well as by size, shape and relations. A few examples from the colour scheme will serve to illustrate the point.

Terra cotta: motor plate, motor nuclei and pyramidal tract.

Red: caudate and lentiform nuclei, extrapyramidal connections.

Gray: intra- and intersegmental structures (association plate).

Light blue: structures composed of sensory neurones of the first order (peripheral nerves, sensory ganglia, mesencephalic root and spinal tract of the trigeminal nerve, tractus gracilis and tractus cuneatus, etc.).

Light green: thalamic structures.

Black: tertiary cerebellar structures (medial longitudinal fasciculus, vestibulospinal and olivospinal tracts).

About fifteen colours of clay may be used; the six colours mentioned above serve merely as examples.

The various steps in reconstruction are as follows. Certain stages are illustrated in Figures 1 to 9.
(a) Sensory and motor endings are drawn on the base board in diagramatic fashion. The afferent and efferent fibers of a spinal nerve are drawn from the endings to the cross section of the spinal cord situated on the raised block which receives the central supporting rod of the model. Cross sections of the spinal cord at representative levels are also drawn on the base board. The various tracts of the white matter of the cord are coloured according to the scheme decided upon for the model.

The completed base board is shown in Figure 1.

(b) The reticular formation which is situated centrally throughout the brain stem is next moulded upon the supporting rod. It will be recalled that the reticular formation is a complicated meshwork of nerve fibers and scattered nerve cells. The reticular formation merges with many surrounding structures but its outlines may be determined with sufficient accuracy from enlarged photographs of brain stem sections stained by the Weigert method.

The motor nuclei are then placed in position in the following order:

(i) Motor nuclei of cranial nerves 3, 4, 6 and 12 which innervate striated muscle derived from myotomes.

(ii) Motor nuclei of cranial nerves 5, 7, 9 and 10 which innervate striated muscle derived from branchial arches and smooth muscle and glands of the viscera.

The completion of this stage is illustrated in Figure 2.

(c) The main sensory nuclei and tracts of the cranial nerves are now placed in position. These include the spinal tract of the trigeminal nerve, the chief sensory nucleus and the nucleus of the spinal tract of the trigeminal nerve and the tractus solitarius with its nucleus. The vestibular nuclei are added at the same stage and the connections of the vestibular nuclei with the medial longitudinal fasciculus represented symbolically.

The completion of this stage is illustrated in Figure 3.

(d) Nuclei and tracts concerned with cerebellar function are added next. These include the dentate, emboliform, globose and fastigial nuclei and the flocculonodular lobe of the cerebellum. The red nuclei and inferior olivary nuclei follow after which the component tracts of the superior and inferior cerebellar peduncles may be moulded into position. The superior peduncle includes the brachium conjunctivum and anterior spinocerebellar tract. The inferior peduncle includes the posterior spinocerebellar tract, olivocerebellar fibers, connections between the vestibular nerve and nuclei with the cerebellum, dorsal external arcuate fibers from the lateral cuneate nucleus and the uncinate fasciculus.
It is useful to use three colours of clay to represent structures incorporated in or associated with the cerebellum in order to distinguish the following three divisions:

(i) Structures associated with the vestibular apparatus (equilibrium),

(ii) Structures associated with tracts carrying impulses of proprioceptive origin by way of the spinal cord (posture and muscle co-ordination), and

(iii) Structures associated with the cerebral cortex-pons-cerebellum-thalamus-cerebral cortex circuit (integration of highly skilled motor activity).

The following sensory structures are now added: nuclei gracilis and cuneatus, medial lemnisci and spinothalamic tracts and structures associated with the acoustic division of the auditory nerve (dorsal and ventral cochlear nuclei, trapezoid body, lateral lemnisci, superior olivary nuclei and inferior colliculi).

An examination of Figures 4, 5a and 5b will help to obtain a mental picture of the model at this stage of its preparation.

(e) The hypothalamus is constructed in such a manner as to show the various hypothalamic nuclei, pituitary body, mammillary bodies and the massa intermedia. The columns of the fornix are placed in position, the remainder of the fornix being added after the thalamus and hippocampus have been constructed.

Figures 5a and 5b illustrate the model after construction of the hypothalamus.

(f) The thalamus and basal ganglia of the cerebral hemisphere (caudate and lenticular nuclei) are placed in position. They are supported by a plywood cross section of the cerebral hemisphere. The hippocampus, fascia dentata and amygdaloid nucleus may be added and the fornix completed. It is possible at this point to continue the medial lemniscus, spinothalamic tracts and brachium conjunctivum into the thalamus and to construct the mammillothalamic tract.

Figures 6a and 6b illustrate the model after these structures have been constructed.

(g) The next step includes reconstruction of portions of the visual system (optic nerve, chiasma and tract, lateral geniculate body, superior brachium and superior colliculus). At the same time the medial geniculate body and the inferior brachium on the auditory pathway are placed in position. Attachment of the chorioid plexus of the lateral ventricle completes this stage of the model.
The model constructed by the writer was terminated at this stage and is illustrated in Figures 7, 8 and 9. It is possible to carry the construction a good deal further to include details of the rhinencephalon, epithalamus, cerebral cortex and the connections of the latter with lower centers.

Neuroanatomical information, unless it is in constant use as a working tool, is added speedily to our forgotten experiences. A careful study of the illustrations may serve to revive old memories.

DISCUSSION

In conclusion a few remarks on the place of the brain modelling method in the medical curriculum may be in order. A stand taken on this subject must be regarded as a personal point of view, based upon one's own experience. I believe that the method has a very definite value at a certain level of instruction. In my opinion the method is not well adapted to an elementary course of instruction during which the student is making his initial contact with the subject. The limited time available for such a course might be used to better advantage in a careful dissection of the formalin fixed brain aided by lectures and demonstrations based on a dynamic conception of the central nervous system. However, for students in the graduate school who are preparing for a career in one of the neurological sciences I can think of no better method of fixing the main relationships of the brain stem structures indelibly in the mind than the personal construction of a model of the brain.

A course in brain modelling has another value in a different direction. The work requires patience and painstaking care. It serves as an excellent test of one's interest in neurology. If interest in the subject is superficial the student soon learns this to be the case and the embryonic brain model undergoes an arrested development at an early stage.

It is with these thoughts in mind that preparation is being made to offer an advanced course in neuroanatomy based upon the preparation of a brain model by each student into the Graduate School of this University.

I wish to thank Dr. Francis McNaughton for his courtesy to me in Montreal and for information regarding the development of brain modelling as a teaching method. Mr. John Lord provided valuable assistance in the practical aspects of the work and Mr. Charles Hodge co-operated in the matter of photography. Additional photographic work was done by Mr. W. F. Maguire, B.A. Mrs. Margaret Corrin prepared the illustrations for publication.
REFERENCES


DESCRIPTION OF FIGURES

Plate 1

**Figure 1:** The base board of the model (x 1/4). The main sensory and motor endings are shown diagrammatically on the left side of the board. They are connected to a drawing of a cross section of the spinal cord by nerve fibers traversing anterior and posterior roots. The fiber tracts of the white matter of the cord are drawn in colour in the composite cross section on the raised block. The latter is drilled to receive the central supporting rod of the model. The board also bears drawings of cross sections of the spinal cord at four representative levels.

**Figure 2:** The central reticular formation has been moulded on the supporting rod. The medial longitudinal fasciculus and the motor nuclei of the cranial nerves have been added. Due to the use of coloured modelling clay the nuclei stand out in good contrast in the actual model. They are shown poorly by achromatic photography. This is a lateral view of the developing model (x 1/6).

**Figure 3:** A dorsal view of the model after certain sensory structures have been added (x 1/4.5). The motor nuclei of the 3rd, 4th, 6th and 12th cranial nerves are seen clearly lying dorsal to the medial longitudinal fasciculus and adjacent to the mid-line. The chief sensory nuclei of the 5th nerve may be seen midway along the model at its lateral edges. The mesencephalic root of the trigeminal passes cranially and the spinal tract of the same nerve with its nucleus passes caudally from the point of entrance of the trigeminal nerve at the level of the chief sensory nucleus. The large paired masses in the lower part of the model represent the vestibular nuclei. The connections of the latter with the medial longitudinal fasciculus are shown symbolically.

**Figure 4:** The midline structures have now been added in plywood in outline. Additional anatomical details have been moulded to this support in clay. The large irregular mass to the right represents the dentate nucleus of the cerebellum. The brachium conjunctivum may be seen as it proceeds forward from the dentate nucleus to cross the midline anteriorly and reach the region of the opposite red nucleus. The flocculus of the flocculonodular lobe of the cerebellum is seen below the dentate nucleus. The posterior spinocerebellar tract is the only component of the inferior cerebellar peduncle which is in place at this stage. The inferior olivary nuclei are clearly visible in the lower part of the brain stem. The large tract which passes vertically between the
inferior olivary nuclei, superficial to the brachium conjunctivum and lateral to the red nucleus, represents the medial lemniscus. The tectospinal tracts are visible between the medial lemnisci as the latter diverge. The rubrospinal tract lies dorsal to the inferior olivary nuclei. This is an anterolateral view of the partially completed brain stem (x \( \frac{1}{8} \)).

**Figure 5a:** An anterolateral view of the brain stem at a later stage (x \( \frac{1}{8} \)). Note the spinal lemniscus situated posterior to the inferior olivary nucleus. It merges with the lateral edge of the medial lemniscus above the olive. The olivocerebellar component of the inferior cerebellar peduncle has been added. The anterior spinocerebellar tract may be seen as it enters the cerebellum by way of the superior cerebellar peduncle. Fibers from the cochlear nuclei are represented symbolically as they pass from the cochlear nuclei to the lateral edge of the medial lemniscus. These fibers traverse the medial lemniscus (forming the trapezoid body) and can just be seen as they decussate in the midline prior to traversing the medial lemniscus of the opposite side. These fibers emerge from the lateral border of the opposite medial lemniscus as a compact bundle, the lateral lemniscus. This tract may be seen clearly as it passes upwards to the inferior colliculus. With regard to diencephalic structures and derivatives, the pituitary body has now been moulded into position, the left mammillary body may be seen further posteriorly and the column of the fornix, the large efferent pathway of the mammillary body, may be seen as it loops over the foramen of Monro.

**Figure 5b:** A lateral view of the model at the same stage of completion as Figure 5a (x \( \frac{1}{8} \)). In addition to the structures already identified the nuclei gracilis and cuneatus may be seen on the dorsal aspect of the lower part of the medulla. The small oval mass situated lateral to the lateral cuneate nucleus represents a nucleus interposed in one of the proprioceptive pathways to the cerebellum. The small strand which emerges from this nucleus to enter the inferior cerebellar peduncle is a symbolic representation of the dorsal external arcuate fibers. The hypothalamic nuclei and above them the massa intermedia have been added to the diencephalon.

**Figure 6a:** An anterolateral view of the model after the addition of a plywood cross section of the left cerebral hemisphere, the thalamus and the basal ganglia of the cerebrum (x \( \frac{1}{8} \)). The large mass, more anteriorly situated, represents the head of the caudate nucleus which is prolonged upwards and backwards as the tail of the caudate nucleus. The large mass situated lateral and posterior to the caudate nucleus is the lenticular nucleus. Note the continuity between the two nuclei ventrally. The cleft which is occupied by the anterior limb of the internal capsule is clearly visible between the caudate and the lenticular nuclei. The
amygdaloid nucleus, which receives the end of the tail of the caudate nucleus, may be seen beneath the lenticular nucleus. The lighter mass beneath the amygdaloid nucleus represents the anterior tip of the hippocampus. The cleft in the plywood cross section of the cerebrum situated just above the tip of the hippocampus represents a cross section through the inferior horn of the lateral ventricle near its anterior end.

Figure 6b: A posterolateral view of the model at the same stage of completion as Figure 6a (x $\frac{1}{9}$). The large mass situated medial to the tail of the caudate nucleus is the thalamus. The posterior portion of the lenticular nucleus just emerges through the plywood cross section of the hemisphere. Note the hippocampus beneath the tail of the caudate nucleus. Note also the fornix and its relation to the thalamus and the hippocampus. The tail of the caudate nucleus is separated from the thalamus and hippocampus by the lateral ventricle.

Plate 2, Figure 7: An anterolateral view of the brain model at a further stage of completion (x $\frac{1}{10}$).

Plate 3, Figure 8: Posterior view of the model at the same stage as that represented in Figure 7 (x $\frac{1}{7}$).

Plate 4, Figure 9: Anterolateral view of the model from the right side at the same stage as shown in Figures 7 and 8 (x $\frac{1}{5}$).

Figures 7 to 9 are labelled in sufficient detail to render any further description unnecessary.
Pharmacological Action of Aminophylline*

A Review of the Literature

By ROBERT H. MARTIN, M.D. (MEDS '46)

The high incidence of coronary artery disease and the high mortality of coronary thrombosis has prompted much investigation into the condition and a great deal of controversy has resulted.

Aminophylline is one of the drugs, the efficacy of which in coronary artery disease is still open to question. Before denouncing or approving this drug it behoves one to present a sufficiently critical background, especially for students, who may become unduly prejudiced before they have had any clinical experience with the drug. With this aim in mind it was decided to air the controversy over this drug, and if possible, reach some satisfactory conclusions.

CHEMISTRY

Aminophylline is actually a proprietary name for theophylline in ethylene diamine. It is also known by several other proprietary names, as, metaphyllin, cardophyllin, and euphyllin. Theophylline is a methylated xanthine of which there are three: caffeine, theobromine, and theophylline. Xanthine is a dioxypurine.

The chemical name for theophylline is 1,3 dimethyl xanthine. It is found naturally occurring in the leaf of the Thea chinensis and is also prepared synthetically. Aminophylline contains 70-85% anhydrous theophylline and approximately 13% ethylene diamine.

HISTORICAL

All studies of the action of the methyl xanthines on the coronary vessels and circulation have been inspired by the observations of Askanazy in 1895 that these drugs alleviated the pain of angina pectoris. It will be noted that clinical results preceded any laboratory experiments. Hedbom, in 1899, did the first experimental work. Using the perfusion method he found that caffeine increased the output from the coronary vessels and also that the rate and amplitude of the heart beat was increased. Eppinger and Hess in 1909 observed a stretching of strips of coronary arteries in a solution of caffeine. From all available information it appears that theophylline in ethylene diamine was first introduced in 1908 when it was noticed that ethylene diamine, a

*At the special Medical Convocation of the University of Western Ontario, held in March, 1946, Dr. Martin received the First Charles R. Will and Company, Limited, Prize for this essay. The prize is awarded to the final year student presenting the best essay in Pharmacology.

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slight coronary vasodilator itself, markedly enhanced the vasodilator action of theophylline.

**DISCUSSION ON ACTION**

In studying the action of aminophylline on the coronary vessels there are two main methods which have been used.

1. Using the isolated perfused heart.
2. Using the intact heart in a living animal.

**USING THE ISOLATED PERFUSED HEART**

In any method of experimentation on coronary flow many factors must be considered in the evaluation of results, such as the blood pressure in the aorta, the cardiac output, the cardiac rate, the amplitude of contraction, and direct vasodilation of the coronary arteries. It must be remembered that perfusion experiments on the isolated heart are peculiar from the intact heart in the living animal in that a constant supply of drug reaches the tissues permitting any amount to be taken up and also that the nerve supply to the heart and vessels has been severed and the peripheral vasomotor responses have been eliminated.

Most workers claim that aminophylline raises the aortic blood pressure. Boyer and Green showed this by optically recording the blood pressure directly in the aorta while administering aminophylline. Wiggers, in 1936, after a series of experiments stated that there was no instance of increase of coronary flow following the intravenous injection of aminophylline which could not be explained on the basis of increased aortic pressure. Yet Heathcote, as early as 1920, recognizing that increased aortic pressure might be acting on the coronary flow, controlled the aortic pressure in his experiments. Using caffeine, theobromine, and theophylline, he perfused each of these drugs through a rabbit’s heart and kept the pressure in the perfusion apparatus constant. All three drugs increased the coronary flow. Heathcote concluded from his results that theobromine was the greatest vasodilator of the three and recommended it over theophylline. The increased flow he thought might be due to the increase in rate and amplitude of the heart which he observed, or to direct vasodilation of the coronary vessels. An increase due to increased amplitude of contraction of the heart was not considered likely to be great. Heathcote seems to have misinterpreted his own figures, however. He used the drugs in 1:2000 to 1:40,000 concentration. In higher concentrations theobromine showed the best results but in concentrations from 1:20,000 to 1:40,000 caffeine showed no results, theobromine very little, and theophylline a 20 - 30% increase in coronary flow. It has been estimated since by measuring the concentration in the blood of a human subject after a therapeutic dose of theophylline that the concentration ranges from 1:25,000 to 1:50,000.
Some workers got a fall in blood pressure with a coincident increase in coronary flow. Smith and Miller found that theophylline increased the coronary flow 50 - 80% with a reduction in blood pressure, especially in the diastolic phase. The increase in the coronary flow became more marked as the blood pressure assumed its original level. Gilbert and Fenn in their experiments observed a fall of both systolic and diastolic pressures with a marked increase in coronary flow, so control of this variable was considered unnecessary.

An increase in the cardiac rate was noted by Hedbom to be one of the actions of the methyl xanthines. Guggenheimer and Sassa, using the isolated cat's heart, found that theophylline and aminophylline increased the coronary flow 40 - 80% respectively. They attributed the 40% increase with theophylline to the acceleration in cardiac rate, but pointed out that with the 80% increase with aminophylline there was only a 10% increase in cardiac rate. Smith, Miller and Graber observed some acceleration in cardiac rate but state that it was not a prominent feature. They found that theophylline augmented the coronary flow 20 - 45% and that the greatest increase was produced when there was no change in cardiac rate. They also found that aminophylline increased the flow 40 - 90% but had a greater tendency to accelerate the heart. With both drugs, however, the increase in coronary output was independent of the accelerating action of the heart as was indicated by experiments in which a uniform rate was maintained by rhythmical electrical stimulation.

Experimental work seems to indicate that aminophylline stimulates the myocardium directly. Heathcote noted that the addition of theophylline to the perfusion fluid resulted in an increase in amplitude of contraction of the mammalian heart. Smith, Miller and Graber, using an isolated rabbit's heart perfused through the aorta, noticed a distinct increase in the excursion of the cardiac contractions when they were recorded on a smoked drum.

There is much evidence in favour of aminophylline causing a direct relaxation of the musculature of the coronary arteries. This seems to be a common finding as can be seen in the work of the men mentioned above. There are some objections to taking the results of perfusion experiments on the isolated heart as evidence of actual coronary artery dilation. However, Gilbert and Fenn, repeating the work of Eppinger and Hess, found a lengthening of coronary artery strips suspended in solutions of the xanthines.

**Using the Intact Heart in the Living Animal**

In a well regulated series of experiments, Essex and co-workers placed thermostromuhr units on the coronary arteries of anesthetized dogs to measure the coronary flow. When aminophylline was admin-
istered in appropriate doses the coronary flow was markedly increased from 15 to 173%. These men even timed the duration of the increased flow and found it to vary from two minutes to 24 minutes. Stoland, Ginsberg, et al., using the intact animal, found the average time of coronary vasodilation to be 21.6 minutes for doses comparable to therapeutic doses in man.

In 1941, Boyer and Green introduced a new note into the controversy when they suggested that most of the vasodilation observed with aminophylline could be due to increased metabolism of the heart. These men studied the rate of inflow at any given moment and the mean inflow into the coronary artery and also simultaneously took an adequate record of the phasic variations of the aortic pressure. All this was done by optically recording on a graph at each instant in the heart cycle, the rate of inflow into the coronary artery together with the aortic pressure. They found that normally the rate of flow increases during the rise of aortic pressure in systole but decreases in the latter half of systole. The rate increases rapidly during isometric relaxation and then declines gradually during the latter part of diastole. When aminophylline was administered, the rate of coronary flow at the end of diastole was increased and the mean flow during the entire cycle was also increased but the drug was found to cause a considerable backflow during the latter phase of systole. Increase in the rate of inflow at the end of diastole was used as an index of the degree of relaxation of the coronary vessels and similarly the change in rate of inflow in the latter phase of systole reflects variations of myocardial compression plus changes in calibre of the coronary vessels. Therefore, they postulated a dual effect due to aminophylline.

1. Decrease in peripheral resistance throughout the cycle caused by dilatation of the vessels controlling coronary flow.
2. Increase in resistance to flow during systole due to an increase in extravascular compression exerted by the contracting myocardium.

Their conclusion was that the vasodilatation could not be solely attributed to the direct action of the drug, for the increased vigor of contraction may, by increased liberation of metabolites, be in part responsible for the vasodilation.

Attacking the problem directly, Fowler, Hurewitz and Smith, in 1935, published one of the most spectacular articles on the problem. These men repeated perfusion experiments on an isolated rabbit's heart and satisfied themselves that aminophylline was the most effective coronary vasodilator. Then, using a series of dogs, they opened the chest cavity of each aseptically and under anesthesia, and ligated the anterior descending branch of the left coronary with its vein just above
the last main branch. Immediately on ligation an area of cyanosis appeared below. In six of these dogs they injected aminophylline intravenously in five minutes following the ligation and observed a regression of the area of cyanosis on the operating table. In the survival experiments nineteen dogs were used, ten as controls and nine were given three grains of aminophylline daily by mouth. At the end of 3 weeks all the dogs were examined. They found a marked reduction in the extent of the fibrosis below the ligation in the treated dogs, on comparison with the untreated dogs, both grossly and microscopically. Their conclusions were that aminophylline promoted the development of the collateral circulation in experimentally induced cardiac infarction in the dog.

Two years later, however, Gold, Travell and Modell published an article on their experiments in which they set out to repeat the work of Fowler and company. Gold claimed that Fowler’s results might be only peculiar to dogs. So, using 52 cats, they ligated the circumflex branch of the left coronary artery; the vein was not included in the ligature. Aminophylline was given in one dose daily of 25 mgms. per kilo intramuscularly. Controls were run at the same time. All animals were killed and examined in three weeks’ time after ligation. Their results were most confusing. They found that the infarct was 18.3% larger in the treated animals than in the untreated animals. They cannot account for this and state that it may have been accidental. Ventricular tachycardia occurred in 47.4% of treated cases and only 8.7% of untreated cases. This did not seem to be related to the size of the infarct but appeared in both small and large infarcts of the treated cases. In microscopic sections of the infarcted areas the treated could not be distinguished from the untreated cases. Healing was not accelerated. These results would indicate that aminophylline makes an infarcted area worse.

Tennent and Wiggers showed that the muscular area supplied by the descending ramus of the anterior coronary artery ceases to contract within one minute after occlusion of its branch, showing that the collateral supply is not enough to maintain contraction in that area. Therefore Wiggers and Green in 1936 concluded that any drug increasing the collateral supply significantly should cause some amelioration of the systolic muscular expansion which occurs and perhaps some sign of contractile recovery. So aminophylline was given one minute after occlusion of the descending ramus of the anterior coronary artery with myographic recordings being made of the occluded area. Results indicated that the collateral blood supply was not improved sufficiently to restore contractions.

More recently, Hall and his associates, showed that on sudden
occlusion of the coronary artery in conscious animals a reflex spasm of the other coronary vessels occurred with a 75% mortality rate. They suggested that this reflex spasm may be due to accumulation of metabolites setting up afferent sympathetic impulses. These initiate efferent parasympathetic vasoconstrictor impulses causing spasm of the medium-sized and smaller coronary arteries and arterioles. On cardio-sensory denervation they found that the mortality rate was reduced to 25%. LeRoy, Fenn and Gilbert, using a similar procedure, reported a mortality rate of 70% due to reflex spasm on occlusion. They also showed that if the animal was saturated for several days before the occlusion with aminophylline the mortality rate dropped to 56%. They attributed this to the aminophylline causing an active dilatation of the coronary vessels giving a protective effect.

**SUMMARY**

From the brief review of the literature just completed, it can be seen that aminophylline has several actions on the heart and its vessels. The main interest of course is in the coronary vasodilating action and the question is whether this is mainly a primary direct action or a secondary result of some other effect of aminophylline on the heart.

The coronary flow is a direct function of the aortic blood pressure and especially the diastolic pressure. There is still a great deal of difference of opinion as to the effect of aminophylline on the blood pressure but mostly it seems to be raised. The matter cannot be truly evaluated in the isolated heart as many factors are not acting. In the intact animal all parts of the circulatory system are affected in some way and in several instances these actions are antagonistic; for example, cardiac stimulation raises the blood pressure while peripheral vasodilation lowers it. The coronary flow, however, increases with aminophylline regardless of whether the blood pressure is raised or lowered. Under constant aortic pressure the flow still increased. The change in blood pressure then has little to do with the increased coronary flow.

An increase in cardiac rate by aminophylline is agreed on by workers with an isolated perfused heart. It is to be expected that since the coronary arteries fill during diastole and are compressed during systole, an increase in heart rate which causes shortening of diastole relatively to systole will decrease the coronary flow. A change within the physiological range of cardiac rate, however, causes little effect upon the coronary flow. Any increase in cardiac rate caused by aminophylline was within the physiological range yet the coronary flow still increased. In the intact animal aminophylline appears to stimulate the medullary vagal nuclei. This may be enough to produce a decrease in cardiac rate so that a slight bradycardia or tachycardia may be observed yet the
increase in coronary flow is independent of either. So this may be dispensed with as causing a secondary increase in coronary flow.

In both isolated preparations and intact hearts the myocardium is directly stimulated by aminophylline. An increase in the amplitude of contraction would increase the cardiac output. However, according to Best and Taylor a rise in cardiac output with a constant aortic pressure exerts a negligible influence upon the coronary circulation.

Any direct stimulation of the heart would increase the metabolism of the cardiac muscle and a compensatory coronary vasodilatation would occur as postulated by Boyer and Green. Undoubtedly this increased metabolism plays a part in the increased coronary flow. However, experiments where the lactic acid content of the coronary blood supply is artificially increased show only a moderate increase in coronary flow. This does not compare with over 100% increase frequently seen with aminophylline. Also there are no products of metabolism acting when coronary artery strips lengthen in solutions of aminophylline.

The claim made by Fowler and co-workers, that aminophylline promoted the development of collateral circulation in the heart, has been much disputed. If the metabolism of cardiac muscle is increased, tending to cause a compensatory vasodilatation and also with a direct vasodilating factor acting on the coronary vessels, I see no reason why the use of aminophylline over a long period of time would not markedly improve the collateral circulation. However, this has not yet been proven. The drop in mortality seen by LeRoy and associates following occlusion after saturation with aminophylline certainly adds weight to this supposition.

CONCLUSION

Aminophylline causes a direct vasodilating action on the coronary vessels.

An increase in the metabolism of the cardiac muscle due to the drug results in a moderate secondary increase in coronary flow.

Aminophylline stimulates the cardiac muscle directly causing an increase in rate, amplitude and output of the heart.

The blood pressure is raised slightly in the majority of cases in the intact animal.

The difficulties of experimentation in this problem have been revealed and the need for more work is clearly seen. Due to these factors the clinical investigation of the use of the drug may be more enlightening than the laboratory results at this time.
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Aminophylline in Relation to Heart Pain

By JOHN F. HARPER, B.A., M.D., (MEDS '46)

Heart pain has been classified by White and Wood under the following headings:

(1) Simple Fatigue Pain which is subdivided into pain caused in—
   (a) Chronic Hypertension
   (b) Aortic Stenosis or Regurgitation
   (c) Mitral Stenosis
   (d) Congenital Pulmonary Stenosis
   (e) Adherent Pericarditis
   (f) Paroxysmal Tachycardia or Paroxysmal Auricular Fibrillation or Flutter
   (g) Permanent Auricular Fibrillation or Flutter with high ventricular rate
   (h) Permanent Coronary Narrowing—Arteriosclerosis

(2) Irritable Heart Pain
(3) Paroxysmal Heart Pain
(4) Pain of Coronary Thrombosis
(5) Aortic Pain
(6) Pain of Pericarditis

In this paper I shall attempt to bring out the various conceptions as to the use of aminophylline (and other xanthine drugs) in the treatment of heart pain.

Askanazy in 1895 was the first man to record the use of a xanthine drug in the treatment of cardiac asthma. In an article dealing with the diuretic action of theobromine sodium salicylate he reported 10 cases with varying pathological changes in which this drug was used for the relief of cardiac asthma and angina pectoris. “By the use of these drugs,” he states, “attacks of cardiac asthma with or without the phenomenon of angina pectoris may be terminated. In some the effect was exceedingly striking.”

Since the time of Askanazy considerable confusion and conflict has prevailed as to the efficacy of this drug in the treatment of heart pain. In 1902 Breuer discussing angina pectoris, said, “In regard to the effect of theobromine I can, on the basis of now, more than 5 years experience only confirm the results of Askanazy throughout and I cannot refrain from saying that I consider his recommendation of

*Dr. Harper received the First Charles R. Will and Company, Limited, Prize for this essay in therapeutics. It is awarded to the final year student presenting the best essay in therapeutics.
Aminophylline in Relation to Heart Pain

Theobromine in the treatment of cardiac asthma and of angina pectoris to be one of the most praiseworthy therapeutic attainments of the last ten years."

There have been many theories propounded as to the mode of action of this drug. Some say that the relief of cardiac pain results from a vasodilatation of the coronary arteries, caused primarily by the drug. Manning, McEachern and Hall in Toronto found that when they occluded a coronary artery experimentally in a dog, there was a reflex vasospasm in the collateral vessels, and in those of the uninfarcted myocardium. With the use of intravenous aminophylline they were able to reduce the mortality of their dogs from 70% to 25%. They found that the infarcted area was smaller in dogs receiving the drug. This work was confirmed by Smith and co-workers and by LeRoy of Chicago.

Others like Starr and his collaborators felt that aminophylline increased the cardiac output and the left ventricular work without increasing the size of the heart. They suggested that the vasodilatation of the coronary arteries was due to metabolites liberated by the myocardial stimulation. Boyer and Green conclude from this that the increase of metabolites liberated in the heart may have produced some or all of the coronary dilation and unless the increase in coronary flow was greater than the increase in cardiac metabolism, aminophylline and related drugs could not be considered effective in increasing the relative blood supply of the heart. Gold, Travell and Modell, working with dogs, measured the size of infarcts caused by experimentally tying off a coronary artery, and found infarcts 18.3% larger in dogs treated with aminophylline than those untreated.

I should like now to analyze the clinical work of several investigators with the view of attempting to reach a decision as to the efficacy of this drug in the treatment of heart pain. LeRoy in a study of 68 patients with angina pectoris gave those patients a course of treatment with sedatives, placebos and aminophylline. The usual dose of aminophylline was 0.2 gm. 3 times per day. If the pain was uncontrolled 0.2 gms. 4-5 times per day was ordered. When 0.2 gms. 3 times per day was satisfactory to control pain, a period of decreased dosage was ordered. The patients were divided into 3 groups, each group being given either sedatives, placebos or aminophylline initially. The choice of medication depended upon the severity of symptoms, their duration and the amount of psychic distress. Placebos and sedatives were never given for more than 2 weeks unless they were definitely beneficial. Aminophylline was administered from 4-10 weeks, the time the drug was given depending upon the severity of the disorder, the efficacy of the drug, etc. There were 17 in the original group receiving sedatives. Of this group 3 patients (18%) received benefit from the drug. In the group which initially received placebos there were 12 of these,
2 or 17\% received benefit. In the aminophylline group there were 39 patients of whom 31 or 79\% received benefit. Benefit here was defined as fewer or less severe attacks of angina pectoris. The 24 patients who received no value from the initial sedative or placebos course were placed on aminophylline. Of the 24 patients, 18 or 75\% received benefit. Following a successful course of therapy with aminophylline 42 patients were placed on a placebo course and it was found 72\% had a relapse. Another group were placed on no therapy and 74\% relapsed. Thus, in general, from this work aminophylline benefited 75\% of patients suffering from angina pectoris, and when patients who had been benefited by aminophylline therapy were given placebos or stopped taking the drug, about 80\% experienced a return of symptoms within less than 3 months.

Levy, Bruenn and Williams carried out a series of examinations on ten patients with known coronary sclerosis. These patients were allowed to breathe an atmosphere of 10\% oxygen and 90\% nitrogen. They were allowed to breathe this mixture first without any medication, so as to accustom them to the apparatus and also to get a series of controls. The idea behind this experiment was, that if a patient with coronary sclerosis were allowed to breathe an atmosphere with a smaller amount of oxygen they would become anoxemic and their anoxemia would cause cardiac pain due to anoxia. The length of time that it took for cardiac pain to appear was charted. Then aminophylline and certain other drugs were given intravenously and the length of time before the appearance of cardiac pain was recorded. Electrocardiograms were also taken and deviations recorded. Aminophylline was given in a dosage from 7-8 mgm. per Kg. of body weight. This caused a prolongation of 63\% in the time of appearance of the pain. In one patient, the pain appeared earlier than in the control. It was noted that deviation of the R-S-T junctions were diminished by 58\%. The T waves were modified significantly in seven of ten cases. In a few cases injection of the drug alone altered the form of electrocardiogram. Injection of an equal amount of salt solution in two cases did not alter the complexes. The heart rate decreased twice, and showed no change eight times. In no case was the heart rate accelerated. The systolic blood pressure rose once, fell three times, and did not change four times. There was no constant relationship between changes in heart rate or blood pressure, the occurrence of angina pain and deviations of the R-S-T junctions. The authors believed the effect on pain and on the electrocardiogram was due to coronary vasodilatation.

Gilbert and Kerr studying a group of 86 cases of angina pectoris used various xanthine drugs. They used theobromine, theobromine sodium-acetate, theobromine sodium salicylate, theobromine calcium salicylate, theophylline sodium acetate and theophylline ethylenediamine.
Aminophylline in Relation to Heart Pain

They gave these drugs for the first three or four days in the week, and then during the remainder of the week, the patients received no medication. This was done for two reasons—first, to avoid nausea and other unpleasant symptoms, and secondly a tolerance is prone to appear in many. In some cases the effect of the drug seemed to last over the intervening days when medication was not used; others complained of more pain during the interval between. The authors have listed the effects of the drugs as no effect, slight effect, moderate effect, and marked effect on pain. Theobromine had no effect on four cases, slight effect on one, moderate effect on six and marked effect on three cases. Theobromine sodium acetate caused no effect on twenty cases, slight effect on one, moderate effect on two and marked effect on thirty-seven. Theobromine sodium salicylate had no effect on twenty cases, slight effect on one, moderate effect on ten cases, and marked effect on thirty-eight. Theobromine calcium salicylate had no effect on seven cases, slight effect on two, moderate effect on three, and marked effect on twenty-seven. Theophylline sodium acetate had no effect on six cases, slight effect on one, moderate effect on five and marked effect on two. Aminophylline had no effect on nine, slight effect on three, moderate effect on three and marked effect on twenty-eight patients. In their series of cases, Gilbert and Kerr were not able to demonstrate any constant changes in blood pressure using these drugs. Occasionally it was slightly lowered. A fall in blood pressure was observed, when theophylline was first administered.

Gilbert and Kerr from their observations found that aminophylline did not seem to be of equal value with the theobromine preparations. Some cases responded to aminophylline which did not respond to theobromine compounds. One case responded to three grains of aminophylline four times a day, after failing to gain relief from one and one-half grains, four times a day. Larger doses give an increased tendency to nausea and nervousness and especially to an increased pulse rate. Toxic symptoms noted by these experimenters were nausea, emesis, burning pain in epigastrium or under the sternum, palpitation, dizziness, headache and nervousness.

Brown and Riseman tested six theophylline, four theobromine and one caffeine preparation on seventeen patients with known angina pectoris. These compounds were tested using the usual clinical methods, and also by measuring the amount of work done under standardized conditions, which could be done without inducing heart pain. The optimal dosage of these drugs was found to be the maximal dosage, which could be given without inducing gastric distress. Not all patients responded to the purine preparations, but it was found that the sodium acetate derivatives of theophylline and theobromine were the most effective. Patients who did not respond to these usually got relief from
theophylline with calcium salicylate. Theophylline, theophylline-ethylene-diamine, mono-ethanolamine, theophylline with methyl glucamine and theobromine with calcium salicylate were about equally effective but less so than the previously mentioned compounds. Theobromine and theobromine with sodium salicylate were distinctly less effective and caffeine citrate was of little or no value. Sedatives are of value in the treatment of angina pectoris but their combination with a purine will not increase a patient's exercise tolerance.

Gold, Kwitt and Otto studied a series of one hundred ambulatory cases in whom the diagnosis of arteriosclerotic heart disease with cardiac pain was made. The study was conducted over a period of five years — the duration of any one case varying from two to fifty months, the average being fifteen. In order to restrict the selection of patients tested, the workers use glyceryl trinitrate tablets of 1/100 or 1/150 of a grain and a soluble placebo taken in the same manner for the relief of pain during anginal attacks. A number of patients found the two tablets equally effective (these were patients who had had coronary thrombosis and were subject to anginal pain on effort). Thus this restriction had to be lifted.

In their study, Gold and coworkers used theobromine in the form of five grain tablets in all cases, and in twelve of them, tests with aminophylline given in one to one half grain tablets were also carried out. The total daily dose of theobromine varied from fifteen to sixty grains given in single doses of five to fifteen grains at intervals of about six hours. Placebos of lactose were used as a control drug. The placebo varied in size, shape and color from the xanthine used. The patients were told that the examiner was uncertain whether the medicine would prove helpful or not, and the future planning of their treatment depended upon the accuracy of their statements.

In their results, Gold Kwitt and Otto found that xanthines had no significant effect upon blood pressure. Electrocardiograms were not taken systematically, but there were nine patients which had tracings taken during their treatment with a xanthine. In these, the forms of deflections, their voltage and the time intervals are indistinguishable from those in the patient’s control tracing. Under treatment with theobromine, they found that sixty-three patients had no change in their pain. With the course of treatment with placebos, sixty-nine patients had no change in their pain. In twenty-two patients, pain was diminished with theobromine and in twenty-five it was diminished with placebos. In fifteen patients, pain was increased with theobromine, and with six patients, it was increased with placebos. The records of one hundred cases were studied, and the results were found to fall into one of four groups.
AMINOPHYLLINE IN RELATION TO HEART PAIN

(a) Those in which the habitual status remained constant, and apparently uninfluenced by any drug (87%).

(b) Those in which a change of status was always for the worse (12%).

(c) Those in which a change of status was always toward improvement (34%).

(d) Those in which the condition fluctuated markedly in both directions.

Evans and Hoyle treated ninety patients with a variety of agents including the xanthines, and their efficacy compared with a placebo. The influence on the pain was determined not only by an estimate of the patient regarding his status, but by a written record kept by the patient of the frequency of attacks. As a result of this work, they stated that they were unable to convince themselves that the xanthines are worthy even of trial in the treatment of cardiac pain.

The rationale behind the use of the xanthines in the treatment of heart pain is significant. Aminophylline has been used for many years as a diuretic drug. Its action upon the kidney is that of a vasodilatation of the renal vessels. It has been used in cardiac asthma with similarly striking results. Stewart and Jack report that aminophylline causes an increased peripheral blood flow. Thus it would seem that aminophylline should be a drug which would logically cause a vasodilatation of the coronary arteries. Confusion has reigned as to the efficacy of this drug in the treatment of heart pain, because of the very nature of the disease. Gold, Kwitt and Otto suggest that spontaneous variations in the course of the pain, changes in the weather, changes in occupation, and the amount of work, changes in diet, changes in eating habits with increase in the amount of rest before and after meals, the condition of the bowels, emotional stress, changes in domestic affairs, the confidence aroused in treatment, the encouragement afforded by any new procedure and a change of medical advisor are all factors which will alter the course of pain associated with the heart. In such a condition it is difficult to assay the value of any drug when there are such numerous variables. Also, not one xanthine drug has been used by investigators, but several. I think there is no question that some xanthine compounds are more efficient than others. And it is my opinion that the xanthine group of drugs as a whole has been derided, because one member of the group has failed to give significant results. Gold, Kwitt and Otto, who are some of the chief debunkers of these drugs, used theobromine in all of their one-hundred cases — and in some used aminophylline. According to Brown and Riseman, theobromine is distinctly of less value than other xanthine compounds. Aminophylline, while effective, is not as effective as the sodium acetate derivatives of theophylline and theobromine. There are other reasons why patients
have failed to show a uniform response to the drug. One must consider
the state of the coronary vessels. If the vessels are rigid and sclerotic,
it is extremely doubtful whether any drug will cause a vasodilatation.
In these people, the use of the drug is bound to fail. Another factor
which Gilbert and Kerr suggests as a possible cause of failure, is that of
tolerance to the drug. If the drug is given successively day after day,
they suggest that the patient will develop a tolerance to it, and its
effectiveness will be cut down or destroyed. All reported experimental
studies agree that the increase in coronary flow produced by the
xanthines, has been transient. It has also been proved by Levy, Bruen
and Williams, that aminophylline given intravenously is more effective
in lengthening the duration of anoxemia tolerated before pain appears,
than is aminophylline given orally or intramuscularly. Thus the drug,
which gives only a transient coronary vasodilatation at best, would
give less in experimental studies in which the drug was given by mouth.

Gilbert uses aminophylline routinely in the treatment of coronary
thrombosis. After he has established the diagnosis, he administers
morphine for pain, atropine 1/100-1/150 of a grain to remove the reflex
vasoconstriction and aminophylline either intravenously or intra-
muscularly. For intravenous use he injects a ten or twenty cubic centi-
meter ampoule containing three and three-quarters or seven and one-
half grains of aminophylline slowly. After the acute emergency is over,
he gives the patient aminophylline orally. These he gives in three grain
doses in enteric-coated tablets or in insoluble calcium salicylate salts of
theophylline. The more insoluble these preparations are, the less likely
they are to cause unpleasant symptoms. If soluble compounds are given,
the alkaloid is precipitated by the acid content of the stomach, or if the
acid is buffered so that the alkaloid is absorbed by the stomach, there
is more chance of unpleasant symptoms. Aminophylline should con-
tinue to be used during the course of the treatment three to four times
a day and for an indefinite period. Auricular fibrillation, auricular
flutter, premature ventricular contractions, or ventricular tachycardia
are not so likely to occur when treatment is instituted promptly. Gilbert
feels that heart block is best treated by aminophylline or papaverine.
Shock is absent or transitory where treatment is begun at once.

CONCLUSIONS

Many workers have found aminophylline and related xanthine
drugs to be efficacious in the treatment of cardiac pain. There are other
workers who heartily disagree and state that the xanthines are of no
value in the treatment of heart pain.

The results of Le Roy using sedatives, placebos and aminophylline
are extremely suggestive that aminophylline has more than just a
placebo-like action. Levy, Bruen and Williams attempting to remove a
variety of variable factors, always associated with cardiac pain (particu-
larly in angina pectoris), used the exercise tolerance of patients with
angina in an atmosphere with reduced oxygen. Although their series
of cases is small and hence their results must not be considered as
universal, nevertheless, using aminophylline they were able to increase
the duration of anoxemia, tolerated before pain appeared by 63%.

The work of Gold, Kwitt and Otto and that of Evans and Hoyle,
is diametrically opposite to the work done by Le Roy — using almost
similar methods. This would indicate that there has been some definite
error, or some factor present, which would cause such a variance of
opinion. With such glowing results as those obtained by Askanazy,
Breuer, Gilbert, Fenn, Musser, Le Roy, Levy, Bruen and Williams
and Kerr, I feel that a patient suffering an acute attack of coronary
thrombosis, or a patient who has repeated attacks of angina pectoris,
should be given the opportunity of treatment with the xanthine group
of drugs. In some, the results will be poor, or of little value, due perhaps
to severe degrees of coronary atherosclerosis, or other factors. But,
until there is more definite proof that the drug is valueless, patients
suffering from cardiac pain should be given aminophylline, or some
related drug.

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The Pharmacology of Penicillin

By CHARLES Y. BROWN, M.D., (MEDS '46)

In 1928, Sir Alexander Fleming discovered that filtrates of the culture liquor of the mold penicillin notatum exerted an antibacterial action on many varieties of bacteria. A decade later, Florey and his colleagues produced a stable, non-toxic preparation of penicillin and showed that it could be used in the treatment of disease in man. The value of penicillin as a therapeutic agent has now been well established.

The precise chemical nature of this new drug is as yet unknown, and it has not been prepared synthetically.

I. ABSORPTION

1. Intramuscular Administration:

The most commonly employed method is to inject one-eighth of the total twenty-four hour dose deep into the gluteal muscles every three hours night and day. It is rapidly absorbed and reaches its maximum titer in the bloodstream within fifteen minutes. Taking 100,000 units as the daily dose the blood level of 0.5 units per cc. is attained in fifteen minutes. The titer falls to 0.1 units per cc. in an hour and below 0.05 units per cc. after two hours. There is only a minute trace after three hours. This method is preferred by most men as it assures a fairly satisfactory tissue concentration, and it obviates the danger of thrombophlebitis which frequently follows the intravenous administration of penicillin.

Continuous intramuscular infusion has been employed, but it has frequently led to abscess formation about the site of the needle.

2. Intravenous Administration:

When penicillin is injected intravenously, the blood concentration rises abruptly and falls equally rapidly. Most workers, therefore, feel that continuous intravenous infusion is better than the intravenous administration of the drug at three hour intervals as the blood titer is maintained at a constantly high level. A continuous intravenous drip of 100,000 units daily will give a blood concentration of 0.2 to 0.1 units per cc. which is adequate for most penicillin-sensitive organisms.

3. Oral Administration:

Penicillin is destroyed by the normal gastric acidity. Vehicles have been used to preserve the activity of penicillin until it has reached the duodenum. It has been shown that a steady, high blood concentration

*Dr. Brown received the Second Charles R. Will and Company, Limited, Prize in this essay in Pharmacology at the special Medical Convocation of the University of Western Ontario held in March, 1946.
can be maintained by oral therapy. The problem at present is to find the ideal vehicle to assure maximum prolongation.\(^6\)\(^7\) Penicillin calcium in peanut oil, and penicillin calcium in citrate have been shown to give therapeutic blood levels.\(^8\)

4. **Subcutaneous Administration:**

Absorption by this route is erratic and variable, and has been thrown into disrepute.

5. **Intrathecal Administration:**

After intravenous or intramuscular injection, penicillin does not pass into the cerebrospinal fluid normally,\(^10\) but appears in small amounts when there is meningeal irritation.\(^11\) However, it may be injected intrathecally or directly into the lateral ventricles in cases of meningitis.\(^9\) Absorption is slow so that it need not be administered more than once in twenty-four to forty-eight hours. Systemic therapy should be given concomitantly.

6. **Rectal Administration:**

Penicillin is inactivated by certain of the intestinal flora, especially Escherichia coli, and no absorption occurs.

7. **Administration by Inhalation:**

Penicillin was found to be rapidly absorbed through the respiratory mucous membrane and to result in highly bacteriostatic blood concentrations. It has been suggested that this method be used in respiratory tract infections and as a prophylactic against secondary pyococcal infections in influenza.\(^22\)

8. **Intra-arterial Administration:**

This method of therapy has been found useful in cases of infection of the extremities. It gives a greater local concentration which results in relief of pain and obviates the necessity of amputation in most cases, or permits lower amputation sites in others. The concentration is increased if a tourniquet is applied to the limb for ten minutes immediately after injection.\(^23\)

9. **Local Administration:**

Relatively small doses of penicillin may be injected into the serous cavities of the joints and pleura in cases of suppurative arthritis and empyema. Absorption is slow and need not be repeated for twenty-four to forty-eight hours.\(^14\)

10. **Topical Application:**

Penicillin may be used in the treatment of infections of the skin and mucous membranes of extensive soft tissue wounds and of compound fractures. The application must be renewed every three to four
hours to be effective. Penicillin should not be used as an irrigating fluid, for, to be effective, several hours of contact are necessary.

II. DIFFUSION

A. Various Body Fluids

When given intravenously, intramuscularly or subcutaneously, penicillin diffuses well into most tissues.

1. Blood:
   Blood plasma contains 90% and the erythrocytes only 10% of the drug on systemic administration.\[14\]

2. Saliva:
   Penicillin enters the saliva, but in smaller concentrations than in the blood.\[15-16\]

3. Cerebrospinal Fluid:
   Penicillin does not enter the spinal fluid on systemic administration, therefore it must be given intrathecally for the treatment of disease of the cerebrospinal system.

4. Ocular Tissues and Tears:
   The usual clinical doses of penicillin exert no antibacterial activity in the tissues of the eye nor in the tears.\[17\] However, following the administration of large doses of penicillin intravenously, penicillin-activity could be demonstrated in the ocular muscles, the aqueous humor, the sclera and the conjunctiva.\[16\] The concentration of penicillin in the vitreous humor and cornea was small and in the lens was lacking. Therefore it is recommended that for the treatment of eye infections, penicillin should be applied locally as well as given systemically.

5. Pancreatic Juice:
   Penicillin does not enter the pancreatic juice following systemic administration.

6. Joint Fluid:
   Penicillin reaches the joint fluid upon general administration in concentrations approximately one-half that found in the blood. This is true for both normal and inflamed joints.\[18\]

7. Pleural Space:
   The systemic administration of penicillin is attended by poor absorption into the pleural space so that disease here should be treated by local instillations.

8. Peritoneal Cavity:
   Penicillin diffuses rapidly into the peritoneal cavity and the concentration rises to a relatively higher level than that which obtains in the blood.\[19\]
B. The Placenta

It has been shown that penicillin diffuses through the placenta and becomes available to the foetus. The concentration present in the umbilical cord is approximately half that found in the mother’s blood.\textsuperscript{18-20}

C. Various Body Tissues

Experiments show that nervous tissues, meninges and bone marrow do not contain penicillin following systemic therapy.\textsuperscript{18} All tissues and fluids excepting bile were lacking in therapeutic concentrations of penicillin two hours after administration.

Concentration of Penicillin in Body Tissues and Fluids After a Single Massive Intravenous Injection

<table>
<thead>
<tr>
<th>Tissue</th>
<th>1 Hour Units/gm. or cc.</th>
<th>2 Hours Time in Hours</th>
<th>3 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>17.38</td>
<td>trace</td>
<td>trace</td>
</tr>
<tr>
<td>Small intestine</td>
<td>9.68</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lung</td>
<td>8.91</td>
<td>trace</td>
<td>trace</td>
</tr>
<tr>
<td>Buccal mucosa</td>
<td>8.39</td>
<td>trace</td>
<td>0</td>
</tr>
<tr>
<td>Bile</td>
<td>6.65</td>
<td></td>
<td>4.99</td>
</tr>
<tr>
<td>Skin</td>
<td>6.06</td>
<td>trace</td>
<td>trace</td>
</tr>
<tr>
<td>Liver</td>
<td>4.77</td>
<td>trace</td>
<td>trace</td>
</tr>
<tr>
<td>Adrenals</td>
<td>2.72</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pancreas</td>
<td>2.69</td>
<td>0</td>
<td>trace</td>
</tr>
<tr>
<td>Heart</td>
<td>2.41</td>
<td></td>
<td>trace</td>
</tr>
<tr>
<td>Voluntary muscle</td>
<td>1.90</td>
<td>trace</td>
<td>trace</td>
</tr>
<tr>
<td>Spleen</td>
<td>1.89</td>
<td></td>
<td>trace</td>
</tr>
<tr>
<td>Nervous tissue</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

III. Excretion

About 60\% is excreted fairly rapidly by the normal kidney, in fact, passage through the human filter turned out to be part of the early process of purification. The intravenous injection of penicillin may be followed by complete elimination at the end of an hour. Following other methods of administration, the rate of excretion is somewhat slower.

It has been shown that the presence of coliform bacteria in the urine decreases rapidly the activity of penicillin, and the higher temperatures of the body tend to hasten its destruction.\textsuperscript{18}

Renal failure acts as a dam so that high concentration of penicillin can be readily maintained in the blood. Attempts have been made to
delay renal excretion of penicillin in man by the use of various substances, but it remains to be decided whether the use of any agent designed primarily to reduce renal excretion would form an undesirable part of penicillin therapy.\textsuperscript{21} Penicillin suspended in an equal mixture of lanolin and corn oil was found to delay urinary excretion.\textsuperscript{15} Measurable urinary levels were found after twenty-four hours. Penicillin modified with aluminum hydroxide or magnesium hydroxide were also found to give therapeutic blood levels.\textsuperscript{12}

The Oxford Investigators demonstrated that penicillin was excreted in the bile and later it was shown to be found in greater concentrations in the bile than in the blood. This suggests that it may be concentrated by the liver.

\textbf{IV TOXICITY}

Penicillin seems to be incapable of causing damage to the liver, brain, kidney or hematopoietic system. Toxic manifestations are rare, but the following reactions have been reported:

1. \textit{Diarrhoea} following systemic therapy, but readily controlled by paregoric.

2. \textit{Mild chill and fever reactions} during the course of treatment.

3. \textit{Thrombophlebitis} at the site of intravenous injection. (It has been shown that penicillin produces alterations of the blood, hastening coagulation and producing a non-retractile clot.\textsuperscript{25}

4. \textit{Pain} at the site of intramuscular injection. (These are believed to be due to chemical impurities in the penicillin and are becoming rarer nowadays.)

5. A number of cases of \textit{urticaria} (2 to 5\%) have been reported, and a case was recently recorded of a purpuric rash preceding the urticarial rash. Some observers believe that the continued use of penicillin in the face of an urticarial reaction will develop into an exfoliative dermatitis.\textsuperscript{24} A study in hyper-sensitivity induced by penicillin showed that 5.5\% of persons injected intradermally with 0.1 cc. containing 1000 units of penicillin exhibited a positive reaction of a tuberculin type. Repeated multiple intradermal injections caused, in some persons, an Arthus type of reaction which developed into a tuberculin type of hyper-sensitivity.\textsuperscript{26}

6. \textit{Mild, systemic reactions} of a temporary nature have been observed following intraventricular therapy, and it has been suggested that penicillin should be given with caution and in small amounts by this route.\textsuperscript{27}

At present there are no known contra-indications to the use of penicillin in the treatment of susceptible infections.
V. Properties of Penicillin

A. Chemical

Penicillin is an unstable organic acid which is prepared as the sodium or the calcium salt. The preparations now on the market are yellow to brown powders which contain about 30% of penicillin. The remaining material which is also extracted from the culture fluid is non-toxic. The powdered penicillin must be protected from heat and moisture, and should be stored in refrigerators until ready to be made into solution. Under such conditions it will retain a potency for six months or longer. Penicillin is destroyed by acids, alkalis, alcohol, certain antiseptics, salts of heavy metals, and certain bacterial ferments (penicillinase).

Both of these penicillin salts are freely soluble in physiological saline or in water. Solutions of penicillin deteriorate rapidly and should be prepared immediately before use if possible, although the solution will retain its potency for about twenty-four hours if kept at refrigerator temperature. The powdered sodium salt is hygroscopic, less stable and apparently more irritating when applied to an open wound than is the non-hygroscopic calcium salt.

B. Anti-bacterial

Penicillin acts through bacteriostasis. Unlike the sulphonamides, which also exert a bacteriostatic action, penicillin is effective in the presence of pus, tissue autolysates or large numbers of bacteria.

Penicillin is highly effective against gram-positive bacteria, both aerobic and anaerobic, Neisseriae and Spirochaetes. It is ineffective against gram-negative bacilli, viruses, acid-fast organisms and yeast-like fungi. Complete tables listing the organisms that are and are not susceptible to penicillin have been published.28

VI. Bio-assay

The potency of penicillin is expressed in terms of Oxford units determined by means of a biological technique. There is no known chemical method of assay. The assay is not exact, there being a possible error of 15%.26

VII. Summary

1. The bacteriostatic effect of penicillin depends on its intimate contact with susceptible organisms. There are at least nine routes of administration which may be used, depending upon the site of the disease.

2. The rapid excretion of penicillin from the body makes it essential that it be given continuously or periodically so that therapeutic blood and tissue levels may be maintained.
3. Penicillin will diffuse rapidly into most tissues when given systematically except in bone marrow, nervous tissue and meninges. For diseases of the cerebrospinal system it must be given intrathecally.

4. The toxicity of penicillin is negligible and should practically disappear when more improved methods of refining the extract are discovered.

5. Penicillin powder should be stored at refrigerator temperature and not made into solution until ready for use. The solutions most frequently used are penicillin sodium or penicillin calcium in water or in physiological saline with or without glucose.

6. Ideal and accurate methods of standardizing penicillin have not yet evolved. Until chemical methods are devised, the individual investigator must select that microbiologic test which is most suited to his laboratory routine. The Oxford or Cup method is probably the one most in use now.

REFERENCES

POSSIBLE WATERHOUSE-FRIDERICHSEN SYNDROME
WITH RECOVERY

By Elvina Anger, M.D.

The so-called Waterhouse-Friderichsen syndrome is one of the most dramatic episodes encountered in medical practice. It is a fulminating infection usually due to the meningococcus with bilateral adrenal haemorrhage. Seventy per cent of the cases occur in children under two years of age. The history, as a rule, is that of a previously healthy child awakening from a peaceful sleep with a cry. Headache, malaise, vomiting and a slight elevation of temperature may be the only initial symptoms of the impending danger. In a few hours, the condition of the patient is critical. Marked cyanosis with peripheral circulatory collapse supervenes with the development of an extensive mottled purpuric cutaneous rash. The child is often in extremis upon arrival at the hospital. Involvement of the central nervous system may or may not occur. At necropsy, bilateral adrenal haemorrhage is present in 95 per cent of the cases.

In 1901, when these symptoms were first recognized, smallpox was considered to be the causative factor. Waterhouse, in 1911, collected 16 cases that presented a clinical picture which he claimed had not been recognized previously but he added nothing to the aetiology of the condition. McLagan and Cook, in 1916, recovered meningococci in two cases of this disease. When Friderichsen, in 1918, summarized the literature, the syndrome assumed its name.

The meningococcus is by far the most common cause of the Waterhouse-Friderichsen syndrome but the recent literature shows that hemophilus influenza, Neisseria flavus 11, strep. hemolyticus, pneumococcus, staph. albus and Friedlander's bacillus may also be the offending agents.

On March 7th, 1945, H. P., a 17-year-old youth, was admitted to the Victoria Hospital, London, Ontario, at 1.45 a.m. The story was that he had had a sore throat the previous day but he had gone to work that morning. By noon, he had developed a severe headache and
malaise and stopped his work. During the evening, a rash appeared, especially on his extremities. The past history was non-contributory. Physical examination on admission, revealed a well-nourished, well-developed young man, who was extremely ill and barely conscious. The temperature was 103.4°F by axilla; the respirations were 40 and the pulse rate 140 per minute. A petechial and purpuric rash was present over the whole body, the lesions being confluent over the arms, shoulders and legs. The pupils were dilated but there was no nystagmus or strabismus. The pharynx was injected. The heart and chest were not remarkable; the blood pressure was 90/60 mm. Hg. The liver and spleen were not palpable. Neck rigidity was not present but Kernig's sign was positive bilaterally. The deep reflexes were active.

A lumbar puncture revealed a cerebro-spinal fluid pressure of 150 mm. of water. The fluid was clear with five cells per cu. mm. The total protein was 40 mgm. per cent. The colloidal gold reaction was unchanged and the globulin content was not increased. A blood culture was taken and intravenous therapy started with normal solution of saline to which was added 60,000 units of penicillin and 5 gm. of solusulfadiazine. The patient received 180,000 units of penicillin with 7 gm. of solusulfadiazine intravenously, daily.

The following morning, the signs of meningismus had definitely cleared and mental improvement was obvious. Myalgia was marked but the purpuric lesions had not increased. During the afternoon retrogression became apparent. The blood pressure dropped to 75/25 mm. Hg. Extreme lassitude was present and the urinary output in 12 hours was only four ounces, although fluids had been taken freely by mouth and over 2000 cc. had been administered intravenously. In view of the oliguria, the drop in blood pressure and the extreme lassitude, 15 cc. of adrenal cortical extract (Upjohn) were injected intramuscularly every six hours. The next day he showed definite improvement and was able to ingest solid foods. The headache had cleared considerably and the rash was beginning to fade. His temperature was 100°F. The urinary output was adequate and the blood pressure rose to 112/68 mm. Hg. On the third day, sulfadiazine was given by mouth; penicillin, intramuscularly, was continued and the adrenal cortical extract was reduced to 5 cc. twice daily. On the fifth day, intravenous therapy was discontinued and he received enteric-coated sodium chloride gr. xv, t.i.d. The purpuric lesions cleared slowly. The blood pressure remained at 110/60 mm. Hg. and the patient was discharged on the 19th day. Subsequently, he returned to work, feeling and appearing well.

LABORATORY EXAMINATIONS

Mar. 7/45—Urine analysis showed a heavy trace of albumin with hyaline casts, red blood cells and pus cells.
White blood cell count 54,000 per cu. mm. CO\textsubscript{2} combining power 51 cc. CO\textsubscript{2} per 100 cc. plasma.
Sedimentation rate 20 mm. in 1 hour.
N.P.N. 40 mg. per 100 cc. of blood.
Blood sugar 93 mg. per 100 cc. of blood.

Mar. 8/45—Plasma chlorides 630 mg. per cent.
Serum sodium 199 mg. per cent.
White blood cells 12,800 (90% neutrophiles and 10% lymphocytes).
Blood culture positive for meningococci.
Stools faintly positive for occult blood.
Sulfadiazine blood level 5.2 mg. per cent.
Serum bilirubin 0.2 mg. per cent.

Mar. 15/45—White blood count 7,150 per cu. mm.
Sedimentation rate 12 mm. in 1 hour.
Serum sodium 300 mg. per cent.
Sulfadiazine blood level 7.7 mg. per cent.

**SUMMARY**

A 17-year-old male with meningococcaemia and purpura improved for 12 hours with chemotherapy and penicillin. Retrogression then became evident and he was given adrenal cortical extract in conjunction with the above-mentioned treatment and uneventful recovery ensued.

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**PULMONARY ACTINOMYCOSIS**

*By Elvina Anger, M.D.*

J.C., a 16-year-old boy, entered the Victoria Hospital, London, Ontario, on December 16th, 1944, with a diagnosis of pulmonary actinomycosis.

The patient lived in a nearby city and had been working in a factory as a cleaner. The past history was uneventful until April, 1944, when he developed a "chest cold" with a productive cough. The cough, with general malaise, persisted, but he continued working until September when he consulted a physician. Between April and September he had lost 25 pounds weight and was admitted to the Queen Alexandra Sanatorium as a case of suspected pulmonary tuberculosis. The sputum was negative for tubercle bacilli; bronchoscopic examination did not reveal an endobronchial tumour but the pleural fluid showed a few fungi suggestive of actinomycosis.

Examination on admission, showed a moderately well-nourished patient with a productive cough and pain in the upper part of the right side of the chest. The physical investigation was negative except for
scoliosis of the spine and the pulmonary findings which included im­paired resonance over the right upper chest, distant breath sounds posteriorly and broncho-vesicular sounds anteriorly over this region. There were fine rales throughout the right upper chest. The temperature varied between 99° and 100°F. The sedimentation rate was 115 mm. in 1 hour and the leukocyte count 28,500 cells per cu. mm. The ray fungus were found in the sputum and the diagnosis of pulmonary actinomycosis was confirmed.

Extensive X-ray and fluoroscopic examinations revealed a massive, almost homogeneous shadow occupying the area of the upper lobe of the right lung. The shadow was most dense in the para-mediastinal parts. By fluoroscopy, it was apparent that the shadow was located posteriorly, behind the hilum. A small barium meal showed two sinus-like extensions into the right lung field at the level of the 6th dorsal spine.

The patient was started on intensive penicillin therapy, 20,000 units every two hours; also sulfamerazine, 1 gm. every 8 hours and potassium iodide as tolerated.

In two weeks, the patient was showing clinical improvement. He had gained six pounds; his cough was less; the pain in the chest became intermittent and only occasional rales could be heard, although the percussion note remained very flat over the right upper chest. The temperature had returned to a normal level. The sedimentation rate had dropped to 38 mm. in 1 hour and the leukocytes to 9,700 per cu. mm. and there was a slight decrease in the density of the chest shadow radiographically. The sinuses could no longer be seen with a barium meal.

Penicillin therapy was continued for 30 days and the sulfamerazine and potassium iodide were administered for six months. Periodical X-ray and clinical studies have continued to show marked improvement of the pulmonary condition.

The last check-up in May, 1945, showed that the patient had gained 30 pounds weight since December, 1944, and X-ray examination revealed only slightly less than the normal transradiancy in the right upper lung field. Clinically, there was nothing abnormal found in the chest. His temperature, sedimentation rate and white cell count were normal. He had returned to work without cough, sputum or pain and felt well.

Pulmonary actinomycosis is generally considered to be a highly fatal disease but in this case treated with a combination of penicillin sulfamerazine and potassium iodide an apparent cure was accomplished.
EVALUATION OF TREATMENT OF ANGINA PECTORIS
By L. M. Hurxthal and W. H. Wilson
of Lahey Clinic
Lahey Clinic Bulletin, 3:237-243, April, 1944

Nitroglycerine—1/200 gr. hypodermic tablet—is by far the most satisfactory treatment for symptomatic relief. As a preventive, a tablet just before the onset of pain is an aid. This drug is rapid in action and almost all authors agree on its degree of usefulness in an attack. In the prevention of an attack, diet, mode of life and rest are all essentials. If the patient is living a high-pressured life, he must learn to relax. His meals should be light and substantial and no gas forming foods should be consumed. Between attacks, anthines, papervine, nitrates and sedatives are often of great aid in decreasing the number and severity of subsequent exacerbations.

Nicotinic acid aids some patients apparently, but probably only those who suffer from an underlying latent deficiency. The drug is given in 300 mgm. doses weekly for a course of six weeks. Iodides are of some value in cases unresponsive to other measures. Potassium iodide, gr. 15 t.i.d. (enteric coated) is administered.

Concerning the use of male sex hormones, since the first report of Edwards in 1939, there have been a number of favorable series reported. The drug may be of special value when the anginal syndrome occurs at the climacteric in the male. Testosterone propionate in 25 mgm. doses is used for 5 to 25 injections.

Cobra venom is of use in some intractable cases. However, its action is slow and hence it is of no value in the active attack unless of the status type. The use of the drug increases the exercise tolerance and improves the daily mode of life of the patient. Electrocardiographic findings show that the drug is not a vasodilator but acts by interrupting the sensory pathways of the heart. Its value lies in this fact and hence should be reserved only for those in whom surgery to interrupt these pathways is contemplated. It may even be substituted for surgery in some cases. Cobra venom does not act well on those responsive to nitroglycerine therapy. The dosage is 10 mouse units t.i.d. the first day, then 1.0 units daily for seven days. This course may be repeated.

Finally, if no relief is obtained from medical measures, surgery may be resorted to. The examples of those operations remaining at present are paravertebral block, Beck's grafting operation and x-radiation to the adrenals. X-rays to the adrenals cuts down on the number of acute discharges of the gland. Some value has been reported for all of these operations.

—Joseph Moody '46

INFECTIOUS MONONUCLEOSIS: A CLINICAL STUDY OF 63 CASES
Annals of Internal Medicine, 23:945, December, 1945.

The authors present 63 cases—61 white, one Chinese and one colored. Of these, 87 per cent were between 18 and 25 years of age. The oldest was 42 years old. In all cases, there was a sporadic type of distribution. These were not isolated, yet no case was contracted on the wards from one of these patients. The incubation period varied between
5 and 15 days. Although two of the cases had their onset with pulmonary manifestations and were at first thought to be cases of primary atypical pneumonia, the majority of patients complained of fever, sore throat, malaise and headache. The authors think that it is quite possible that the pulmonary lesions were manifestations of infectious mononucleosis because it is not unusual to find a normal differential count or even a polynucleosis in this disease. Two patients complained only of "hives" and two others only of diarrhea. All four of these had a generalized adenopathy.

The majority of patients complained chiefly of a sore throat with an admission diagnosis of either nasopharyngitis or tonsillitis. Fever was present in all but seven cases. It followed no particular pattern, was usually of the intermittent type, and although it usually ranged between 101° and 102°F., in several cases it rose to as high as 104°F. The febrile state lasted from one to 35 days—usually longer than six days. To compare this with nasopharyngitis and tonsillitis, the authors reviewed 60 cases of each and found that in all cases the longest duration of fever was five days and that in over 80 per cent the fever lasted three days or less.

On admission, the pharynx was found to be normal in seven cases, inflamed in 27, and associated with a follicular or membranous type of tonsillitis in 20 cases. In the nine other patients, there was noted the development of an acute tonsillitis. Adenopathy was present in all patients during the period of hospitalization, involving the cervical nodes alone in 20 cases and being generalized in the others. The spleen was found to be enlarged in 16 patients. One patient developed jaundice; seven patients had skin manifestations of a transient maculopapular character.

The leukocyte count varied from 3,900 to 48,000 cells per cubic millimeter. Forty-four per cent of the patients had a total white blood count below 11,000 cells. It is the findings of the blood smear which are so characteristic of the disease and upon which the diagnosis rests. In this series, the diagnosis was not made without a typical blood smear, namely, less than 40 per cent neutrophilic cells and the presence of so-called atypical lymphocytes. Several days may elapse before the appearance of these characteristic cells. Second in importance to the typical blood smear findings is the Paul-Bunnell heterophile antibody test, which these authors consider a titre of 1:112 or over to be diagnostic. In this series, 77 per cent of the cases had a positive heterophile agglutination; 70 per cent showed a positive agglutination within the first two weeks of the illness although one test remained negative for 51 days.

One of the most striking features of infectious mononucleosis is the wide variability in the type and severity of its symptomatology. The diagnosis should be considered, in the opinion of the authors, in patients with unexplained fever, unexplained jaundice, splenomegaly, lymphadenopathy and in cases of lymphocytic meningitis. A positive Paul-Bunnell test, while desirable, is by no means essential to the diagnosis. Every case of pharyngitis or tonsillitis which does not respond in four or five days to symptomatic therapy, and especially if associated with adenopathy, should be investigated for the possibility of infectious mononucleosis.

Therapy is symptomatic, with rest in bed during the febrile period.

—Arthur Egler '47

PREFRONTAL LOBOTOMY

By Walter Freeman, M.D., Ph.D., F.A.C.P., and James W. Watt, M.D., F.A.C.S.

The American Journal of the Medical Sciences, 211:1, Jan. 1946.

Prefrontal lobotomy is used in the treatment of intractable psychoses and neuroses which failed to respond to long courses of more conservative measures such as metrazol, insulin or electroshock. The report deals with 311 patients who were followed for periods of six months to nine years after prefrontal lobotomy was performed.

The incisions in the frontal lobes interrupt the anterior thalamic radiation and produce degeneration in the nucleus mediales dorsalis of the thalamus. Studies indicated that the frontal lobes are concerned with foresight and insight, particularly as related to the self. It is in relation to these ego functions that the thalamus is of importance for the adjustment of the individual in his social environment.

Most of the incisions are made in the
plane of the coronal suture, although no ideal plane has been established. There are several factors influencing the decision as to where to make the incision, but the most important is the duration of the psychosis. The psychosis is accepted as being the pathologic stabilization of synaptic patterns among various cell groups. The spread of stabilization is in a posterior direction and comes to include mechanisms concerned in social adaptation. Prefrontal lobotomy fails in deteriorated cases because the operation cannot be carried out sufficiently far posterior to interrupt the psychosis without extinguishing the emotional factors making for a satisfactory adaptation in a normal social environment.

Patients who have been operated on are far from healthy at first. They have exchanged one form of abnormal behaviour for another. The emotional intensity of the psychosis gives way to emotional shallowness and the imaginative activity is reduced. The patient may still have the same hallucinations and delusions but he is no longer bothered by them.

The results of this operation are favorable in obsessive tension states, hypochondriasis, intractable psychosomatic conditions. They are less satisfactory in schizophrenia. Of the entire group, one half were usefully occupied, one quarter were at home and the remainder were dead or in institutions. The operation is ineffective in chronic alcoholism, epilepsy and parkinsonism. Sequelae occur in a minor percentage of cases which include inertia, aggressiveness and epileptic seizures. The operation is relatively safe, the mortality being less than three per cent, and it can be carried out in patients whose physical condition contraindicates other drastic forms of treatment.

—MARY MURPHY '47

POSTOPERATIVE PROPHYLAXIS OF RECURRENT MAMMARY CANCER WITH TESTOSTERONE PROPIONATE

By ANTONIO PRUDESTÉ, M.D., MAJOR ARMY RESERVE, SÃO PAULO, BRAZIL


The author discusses the subject in a very orderly manner. He first deals with endocrine dysplasias as related to breast pathology; then breast pathology as related to malignancy and the rationale in the treatment of breast cancer by means of male hormones.

In essence, he attempts to show that:

(a) The mastopathies and, as a further stage, cancer, are related to hyperestrinism;

(b) Testosterone is the antagonist of estrin—hence the rationale in treatment and prophylaxis of the postoperative recurrent mammary cancer by means of the male hormone.

The observations on a series of cases of mammary cancer in which testosterone was used post-operatively are given along with a series of cases in which no post-operative hormone therapy was administered. One might conclude from the article that testosterone is not the complete answer to the prevention of recurrence of breast cancer, but that it is another important aid in making the burden of the unfortunate victim somewhat easier to bear.

THE CRITICALLY BURNED PATIENT

By JOSEPH C. URKEY, M.D., CHIEF OF PLASTIC SURGERY SECTION, AMERICAN HOSPITAL, CHICAGO.


Treatment should be instituted before signs and symptoms of a critical condition appear. Therefore, if there is any doubt as to the patient’s condition, treatment should be started.

The initial treatment involves:

1) the control of pain using
   a) Morphine—as much as ¼ grain may be given in one hour.
   b) Codeine Sulphate—½ grain three times daily.

Barbiturates are contraindicated since they may increase toxicity.

2) the prevention of tetanus
   1,500 units are given following a sensitivity test.

3) initial treatment of the burn
   a) debridement should be minimal and cleansing gentle.
   b) the use of tannic acid is contraindicated as it is toxic to the liver.
   c) two types of dressing may be used: i) plaster—has the advantage of protection and immobilization, but is hard to remove.
ii) pressure—is the dressing of choice. It is composed of gauze, waste cotton and roller bandage. A wet pack is best since it will not slip. An elastic crepe bandage is contraindicated. Some type of grease application is placed next to the skin.

4) the control of shock

The danger of shock lasts for two to three days. Fatality is likely to occur due to oedema of the lungs. Plasma transfusions are started at once. From 3,000 to 6,000 cc. are given within the first 48 hours. Equal amounts of an isotonic solution containing sodium chloride, sodium bicarbonate and glucose are given to prevent dehydration and anuria and to restore the electrolyte balance. Oxygen should be administered for the first 48 hours.

The treatment of the period of toxæmia, sepsis and granulation: The period of toxicity usually abates during the first two weeks. The treatment consists of the administration of whole blood and the control of the electrolyte balance. Transfusions of 500 cc. should be given three times a week and when needed daily. Sulpha drugs are contraindicated because of possible reactions to the drugs and anuria. Penicillin is given systematically. It is too irritating for local application.

Types of grafts used are:
1) homograft—used if patient is too ill for surgery.
2) autograft—three types.
   a) stamp
   b) patch
   c) strip

---LILLIAN FULLER '47

MICRO METHODS OF ESTIMATING PENICILLIN IN BLOOD SERUM AND OTHER BODY FLUIDS

By ALEXANDER FLEMING, M.B., F.R.C.S., F.R.C.P., F.R.S.


In this article Alexander Fleming describes two methods for performing micro-titrations of penicillin in the body fluids of patients who are being treated by the drug. In these methods, slide cells or capillary tubes are used as the cultural vessels, haemolytic streptococcus as the test organism, and blood as the indicator.

There is no chemical test for penicillin in blood but the concentration of this substance in blood serum can readily be estimated by titrating its bacteriostatic power on a suitable test organism.

The test mixtures are incubated in either slide cells or capillary tubes. The test organism, the haemolytic streptococcus, must have its sensitivity standardized and the indicator, human blood, must have the leukocytes removed as they themselves have considerable bacteriostatic power.

When the slide cells are used the end point is sharp and definite. Where there is enough penicillin in the serum to inhibit the streptococci the blood is unchanged. In the cells in which the streptococci grow freely, the blood is completely hemolysed. Frequently there is a cell between these extremes where the streptococcal growth has been partially inhibited and hemolysis is only partial.

When the capillary tube method is used, the tubes are examined against a black background and it is usually easy to see whether haemolysis has occurred or not.

Very consistent results are obtained by these methods.

These methods can also be used to estimate penicillin in other body fluids and are especially valuable in those cases in which only minute quantities of fluid can be obtained from the patient. Pus can also be tested by centrifuging it first and titrating the supernatant fluid. The presence of the staphylococcus or organisms other than a hemolytic organism or a penicillinase producer, does not interfere with the test.

---LOIS M. PLUMB '46

PHYSOSTIGMINE FOR MUSCLE SPASM IN ARTHRITIS


Following the use of neostigmine for the relief of the muscle spasm of poliomyelitis, it was decided to attempt the use of physostigmine in cases of rheumatoid arthritis and other allied con-
ditions in order to prevent (or lessen) deformities, and to relieve pain. The authors point out that there is muscle spasm about an arthritic joint and "this spasm remains even though the joint process has become quite inactive." The investigators believe that neostigmine has a direct depressive action on the spinal cord because of the prompt alleviation of pain. As a control, injections of normal saline, and of atropine, were given before the therapy of physostigmine combined with atropine was begun. Of fourteen cases of rheumatoid arthritis treated, none were improved by saline, one was improved by atropine, eight were improved by physostigmine plus atropine (1/100 grain of each injected daily) and four cases showed no improvement at all. Of 153 cases of rheumatoid arthritis treated in the same manner, in the arthritis wards of the Philadelphia General Hospital, 120 improved and 33 did not improve. Several specific cases and their treatment were described, e.g., a case of Felty's syndrome (a special form of rheumatoid arthritis with splenomegaly, leukopenia and pigmented spots on the skin) in a 21 year old female, weighing 82 lbs. was treated with physostigmine. There was a contracture of the right knee with spasm of the hamstring muscles. The therapy caused the muscles to relax, and permitted greater flexion and extension of the knee-joint. When saline therapy was substituted, there was a relapse. When improvement in the contractures ceased, a blood transfusion was given and insulin administered to improve the appetite and increase the body weight. This was followed by a course of gold therapy for a month and a half, using intramuscular aurothioglucone. The patient was able to return to her former occupation eight and one half months after treatment was begun. She now weighed 117 lbs. and had made a complete clinical recovery. Cases of spondylitis of fifteen years duration, sacro-iliac arthritis with sciatica of twelve years duration, osteoarthritis, calcified bursitis, and scalenus anterior syndrome were successfully treated by the use of physostigmine. A complete description of each case is given. Physostigmine was used successfully for the relief of muscle spasm in rheumatoid arthritis and associated conditions. It caused relaxation of muscle spasm even though the spasm had persisted many years. This allowed easier active and passive movements of the joints. The effect of physostigmine is rapid (occurs within three to fifteen minutes) and may persist for several days. It is cheap and does not produce severe toxic reactions. It relieves pain and prevents deformities.

—ELDON MEREDITH, '47

THE USE OF HUMAN IMMUNE SERUM GLOBULIN IN INFECTIOUS HEPATITIS


Prior to the work of Stokes and Neefe indicating the value of gamma globulin from pooled human plasma in the prevention and attenuation of infectious (epidemic) hepatitis, no method of control of outbreaks of this disease was available. The great incidence and lengthy period of convalescence following this disease has made it of prime importance to the armed services of all the United Nations. Experiments were conducted in the Mediterranean theatre of operations, using regiments and bombardment groups of the U.S. command. It was shown that the intramuscular injection of 10 cc. of globulin over a two-day period protected the individual from contracting epidemic hepatitis for at least eight weeks.

—C. Y. BROWN, '46
PEDIATRIC X-RAY DIAGNOSIS

By JOHN CAFFEY, A.B., M.D.

(The Year Book Publishers, Inc., Chicago, 1945)

Only a few textbooks dealing specifically with pediatric X-ray diagnosis have been published in 50 years of diagnostic roentgenology. There was, until now, only one such book in the English language, published as far back as 1910 by Thomas Morgan Rotch, then professor of pediatrics at Harvard University. The modern pediatrician had to rely on general textbooks of radiology when seeking for information on roentgen diagnosis in children’s diseases. For the specialist in roentgen diagnosis there was often reason to regret the absence of a modern textbook on pediatric roentgenology. The peculiarities of appearance of the normal growing bone for example, and of the diverse pathological conditions involving it have found only sketchy treatment in most general texts on roentgen diagnosis, necessitating often a cumbersome search for special publications and references in the general and pediatric literature as well as in works on normal and developmental anatomy. The same holds true with numerous other pathological conditions peculiar to infants and children. The appearance of a modern textbook on pediatric X-ray diagnosis will, therefore, arouse considerable interest among pediatricians and radiologists alike, because it remedies "a literary developmental hypoplasia," to borrow a phrase which the author uses himself in the foreword.

The ways by which the clinician and the radiologist approach roentgen diagnostic problems are by necessity often diametrically opposite, although the establishment of an exact clinical diagnosis is the aim of both. The fact that the author, associate professor of pediatrics at Columbia University, is at the same time an expert radiologist gives this book its peculiar value and flavour. It follows a happy synthesis of clinical-radiological experience with fundamental general roentgenological analysis. A wealth of information on important principles of general roentgenological interpretation as well as clinical appraisal of roentgen findings give this new book a far greater value than it would
have were it merely a source of information for the pediatric specialist. It will be read with equal gain by anyone interested in, and pondering over roentgen diagnostic problems in general.

The presentation of the normal anatomy and of diseases of the growing bone, the relation of radiological appearance to normal anatomical structures and pathological disturbances occurring in various bone diseases, comprises, perhaps, the best, most informative, and most original chapters of this book, but the presentation of the other parts of the book is equally well done and based on the author’s large personal experience and knowledge of the general radiological literature.

The chapter on thorax contains a wealth of information regarding general radiological interpretation, especially in the differentiation of the various shadows and transparencies composing the normal chest radiograph. The differentiation and localization of pulmonary, bronchovascular and pleural, including interlobar shadows, if masterfully presented and superior in many respects to anything in other available modern textbooks on roentgenology, quite apart from a detailed discussion of clinical entities and clinical evaluation of radiological findings in pediatric diagnosis. The reproduction of more than 700 representative radiographs and most instructive sketches is excellent.

Every student looking for information and guidance in the ever increasing field of modern X-ray diagnosis in general, will greatly profit by consulting this excellent work which fulfills in the best sense what it promises to be in its sub-title: “A textbook for students and practitioners of pediatrics, surgery, and radiology.” As such it will take its place among the best which modern literature has to offer.

—A. Bernstein, M.D.

"OURSSELVES UNBORN"

By George W. Corner

(Yale University Press, 1944, 188 pages, $3.00)

This volume is based upon the twenty-first series of lectures delivered at Yale University on a foundation established by the late Dwight H. Terry of Bridgeport, Connecticut.

The author presents a brief description of human development, its biological significance, and its aberrations, taking into account many recent discoveries related to the “philosophy” of embryology.

The first of three parts into which the book is divided — “The Embryo as Germ and as Archive”—deals with human embryology from fertilization to birth.
The second part—"Prenatal Fate and Foreordination"—lists numerous factors encountered in prenatal life which influence the individual in post-natal life. Nutrition, uterine infection, irregular fertilization and genetics are among those factors considered.

The third part—"The Generality and the Peculiarity of Man"—bodily shows the relationship between man and other animals as seen in the development of each.

This book has a special value, aside from its technical information, in its power to stimulate thought—an attribute of no small worth.

—JOHN A. DUFF '49

RED BRICK UNIVERSITY

By BRUCE TRUSCOT

RYERSON PRESS, TORONTO, $3.50)

This is a comprehensive and intensive history which should be read by every student who intends to obtain something more than a mere technical training from his years of university life. The author has presented an extremely interesting and controversial picture of the two university systems which exist in England today. It is an enlightening contrast between the old and venerable schools of Oxford and Cambridge and the many new universities which have come into being in the larger centres of the country.

There is brought to our attention something which should be kept constantly in the minds of all those who have to do with the government of any university, be it in England, America or anywhere else in the world. This is the basic fact that the primary purpose of a university is a two-fold thing: first, research; second, teaching.

Mr. Truscot's definition of a university is extremely interesting. It is his conviction that "a university is a corporation or society which devotes itself to a search after knowledge for the sake of its intrinsic value." The word "intrinsic" is the key word of his definition and its meaning should never be lost sight of during a student's undergraduate or post-graduate years. Everyone who is interested in university life, whether he is preparing for college, at college or a graduate, can gain a great deal by spending a few hours in contemplation of the ideas presented in Red Brick University.

—ALLAN WOOLEVER, '47
"PULMONARY EDEMA AND INFLAMMATION"
An Analysis of Processes in the Formation and Removal of Pulmonary Transudates and Exudates.

By Cecil K. Drinker, M.D., D.Sc.

Professor of Physiology, School of Public Health, Harvard University, Boston, Massachusetts.

The Nathalie Gray Bernard Lectures delivered at Bowman Gray School of Medicine, December, 1944, together with a fifth chapter on Artificial Respiration.

(Cambridge, Mass., Harvard University Press, 1945, 106 pages, 20 photographs, $2.50)

Embracing as it does a topic so old, so vital, and of such constant occurrence, this book offers to students of pathology and medicine a stimulating discussion. In five short chapters, Dr. Drinker traces methodically the structural and physiological characters of pulmonary edema and inflammation together with the principles of their treatment.

The first chapter deals with the histological and gross anatomical considerations involved, with special attention to the part played by the lymphatics. Free use is made of the description of various experiments which have contributed to the present-day concept of the processes.

The next two chapters concern the physiological factors which enter into the picture — the pressures involved, the obstructive factors, and the relationship between type of breathing, body position, and edema.

The last two chapters contain a discussion of therapeutic measures, with the devotion of a special chapter to the subject of artificial respiration. In this matter Dr. Drinker does not hesitate to take sides and to give personal opinions. This attitude prevails throughout the book, and perhaps is the chief factor in producing a readable book rather than a dry reference text.

His main theme in therapy is that "Anoxia begets anoxia," and an early intervention into this vicious cycle is to be practiced above all.

The reading time is only a few hours, and the style is pleasing. Since it treats in all its structural, physiological, pathological, and medical aspects a subject usually spread in bits and pieces into many books, Dr. Drinker's treatise is highly recommended.

—Cameron Wallace '48
The purpose of this review is to bring to your attention a series of valuable works published each year as Proceedings of the Association for Research in Nervous and Mental Diseases. The Association meets annually in New York City in late December. During the previous year a subject for discussion is chosen and various workers in that particular field present papers before the gathering on aspects of the subject with which they have had personal experience. These papers include anatomical, embryological, physiological and biochemical aspects of the subject under consideration as well as the clinical applications of these aspects. The contributors to the discussions represent practically all the outstanding neuroanatomists, neurophysiologists and neurological clinicians both medical and surgical in the North American continent; frequently men from Europe as well present the results of their work concerning subjects under discussion.

The most recently acquired volumes of this series at present in the library are those outlined above.

(a) The volume dealing with the hypothalamus, covers every aspect of that interesting region known up to December, 1939. The list of contributors to this volume is almost an enumeration of modern neurology's Hall of Fame. It is divided into three sections. Part one, the anatomy of the hypothalamus, details all the information as of that date regarding structure. The second section on the physiology of the
hypothalamus outlines in a complete manner the influence of this region on almost every phase of our normal and abnormal activity. The third section comprises the clinical symposium in which most of the interesting observations regarding disease of this region in the human being are summarized.

(b) The next volume concerns the basal ganglia which formed the subject of discussion of the Association in 1940. The basal ganglia have for many years been the neurologists' ping pong ball, one function after another having been ascribed to various of these nuclei only to be discounted at a later date. However, most recently the facts seem to be falling together like the well fitting pieces of an intricate jigsaw puzzle and within a few years we shall perhaps be able to assign a very definite place to these nuclei in the regulation of motor activity.

(c) The third volume—"Pain"—represents proceedings of the Association in 1942. Most of the recent data and viewpoints regarding pain are brought together in this book. The discussions on headache and cardiac pain are of particular interest.

(d) Finally the most recent volume—"Trauma of the Central Nervous System"—constitutes the proceedings of the Association in 1943. This is an extremely important work concerning pathology, diagnostic considerations, electroencephalographic changes, treatment, and sequelae of central nervous system injury. This is perhaps one of the best summaries of this broad and important topic to be found anywhere.

These books are not the type which should be read from cover to cover by the medical student. However, familiarity with their contents and with the broad trends of neurological thought which they represent, together with more complete perusal of specific sections will certainly make his understanding of the nervous system more complete, and they are deserving of his attention.

—A. S. DOUGLAS, M.D.
To Study the Phenomena of Disease without Books

Is to Sail an Uncharted Sea.

--Oseir.

RECENT ACCESSIONS TO THE MEDICAL SCHOOL LIBRARY

Adriana: The chemistry of anaesthesia. 1946.
American foundations and their fields. 1942.
American Medical Association: Council on physical medicine. Handbook of physical medicine. 1945.
Andia. Andanzas de un alienista. 1944.
Arenson: Introduction to quantitative analysis. 1944.
Barnes: Society in transition. 1942.
Beckman: Treatment in general practice; 5th ed. 1945.
Block and Bolling: Amino acid composition of proteins and foods. 1945.
Bourne and Williams: Recent advances in obstetrics and gynaecology; 6th ed. 1945.
Brain and Strauss: Recent advances in neurology and neuropsychiatry; 5th ed. 1945.
Brock: Basis of clinical neurology; 2d. ed. 1945.
Cabot: The doctor's bill. 1935.
Caffey: Pediatric X-ray diagnosis. 1945.
Cassidy: Public health and welfare reorganization. 1945.
Cobb: Foundations of neuropsychiatry; 3d. ed. 1944.
Corner: Ourselves unborn. 1945.
Courville: Pathology of the central nervous system; 2d. ed. 1945.
Doreus and Shaffer: Textbook of abnormal psychology; 3d. ed. 1945.
Drinker: Pulmonary edema and inflammation. 1945.
Ehlers and Steel: Municipal and rural sanitation; 3d. ed. 1943.
Encyclopaedia Britannica world atlas. 1945.
Fisher: Treatment by manipulation; 4th ed. 1944.
Flagg: The art of resuscitation. 1944.
Fuson: A brief course in organic chemistry. 1941.
Glasser: Dr. W. C. Rontgen. 1945.
Golden: Radiologic examination of the small intestine. 1945.
Hamblen: Endocrinology. 1945.
Handbook of chemistry and physics; 29th ed. 1945.
Haymaker and Webb: Peripheral nerve injuries. 1945.
Hewer: Recent advances in anesthesia and analgesia; 5th ed. 1944.
Holmes: The friends of the insane. 1911.
Howe: Neural mechanisms in poliomyelitis. 1942.
Jackson and Jackson: Diseases of the nose, throat and ear. 1945.
Keefer: A textbook of military hygiene and sanitation. 1917.
Keys: The history of surgical anesthesia. 1945.
Kuntz: The autonomic nervous system; 3d ed. 1945.
Lewis: Exercises in human physiology. 1945.
Lowy and Harrow: Introduction to organic chemistry. 1932.
Lyons: The Royal Society, 1660-1940. 1944.
McBride: Disability evaluation; 3d. ed. 1942.
McClure: Functional activities of pancreas and liver. 1937.
McCombs: Internal medicine in general practice. 1944.
McDonough: Poet physicians. 1945.
Marshall: Laboratory guide in elementary bacteriology. 1945.
Minnitt: Gas and air analgesia; 2d ed. 1944.
Rasmussen: Principal nervous pathways; 3d ed. 1945.
Rice: Introduction to biology. 1935.
Rich: The pathogenesis of tuberculosis. 1944.
Sherman: Intelligence and its deviations. 1945.
Shermway: Introduction to vertebrate embryology, 4th ed. 1942.
Thomson and Miles: Manual of surgery; 9th ed. 1939. (2 v.)
Turner: Modern operative surgery. 1943. (2 v.)
Umbrecht, Burris and Stauffer: Manometric techniques and related methods for the study of tissue metabolism. 1945.
U.S. National Institute of Health: Division of public health methods. Tuberculosis in the United States, graphic representation, 1943-44. (2 v.)
U.S. National resources planning board: Human conservation. 1943.
Walshe: Diseases of the nervous system; 5th ed. 1945.
Walter: Biology of the vertebrates. 1943.
War wounds and injuries, ed. by R. Maingot; 2nd ed. 1944.
Wolf and Wolff: Human gastric function. 1943.
Unwilling to reveal, even to a physician, the presence of any abnormal rectal condition—and too often dreading surgery—those who suffer from hemorrhoids do so in silence. Whenever nonsurgical treatment is indicated Anusol will be found a safe, sane and effective therapeutic treatment.

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When writing advertisers please mention University of Western Ontario Medical Journal.
Dean Hall, among his many innovations at the Medical School, inaugurated in April, 1945, the Medical Alumni Lectureships. Twice yearly, outstanding scientists and clinicians are invited to spend the better part of a week, giving lectures, clinics, and conducting ward walks and demonstrations. The small honorarium tendered the visitor is financed by the Medical Alumni Association.

We have been fortunate in securing such outstanding teachers and scientists as Dr. J. Meakins, professor of medicine, McGill University; Dr. Roscoe Graham, associate professor of surgery, University of Toronto (and he recommends fishing as a form of relaxation and Dean Hall agrees), and Dr. Paul White, the internationally-known heart specialist of Boston.

The attendance of the alumni and doctors of Western Ontario and their letters of appreciation indicate that Western is fulfilling one of her obligations to the medical profession and through them to the public. In addition to the students and doctors from London and Middlesex County, 92 doctors from 27 cities, towns and villages, including doctors from every one of the 14 counties in Western Ontario, and others from as far west as Winnipeg and as far east as Montreal came to hear Dr. White. The auditorium with a seating capacity of 330 was inadequate to accommodate all who were in attendance.

According to our records, Western is the only Canadian university that offers such an unique forward step in medical education. Then, too, can you imagine the benefits the lecturer receives? His students will benefit from the stimulation and inspiration that he received as a result of his visit to Western.

J. W. Crane, M.D.