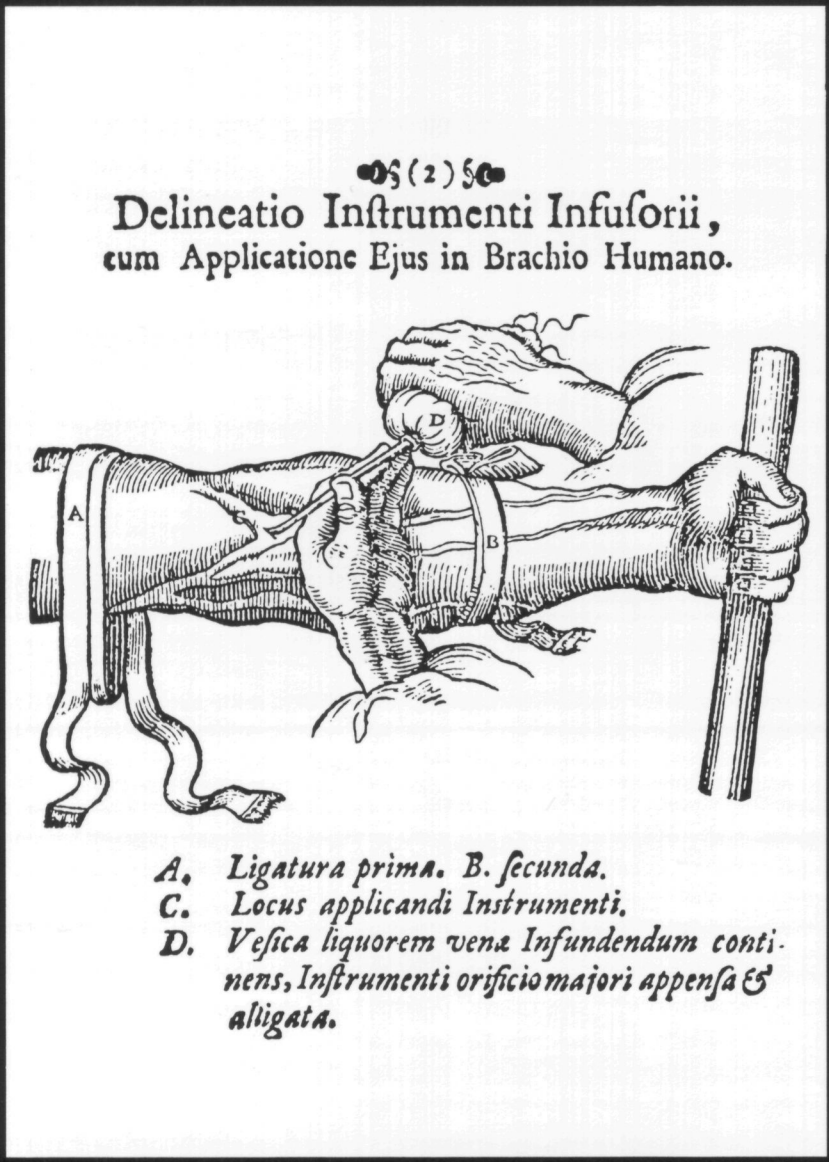
The History of Anesthesiology

Reprint Series: Part Twelve



INTRAVENOUS ANESTHESIA

Illustration from Johann Daniel Major's Chirurgia Infusoria, placidis CL: Virorum Dubiis impugnata, cum modesta, ad Eadem, Responsione. Kiloni, 1667.

The History of Anesthesiology

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INTRAVENOUS ANESTHESIA

Although the roots are deep, extending back into the 17th century, the intravenous injection of drugs for anesthetic purposes became a practical technique only in the 1930's. Even so, the agents employed then were designed to induce rather than maintain anesthesia. And today in contrast to the inhaled vapors, no single compound injected into the blood stream can provide all of the desiderata of surgical anesthesia: lack of awareness, obtundation of reflex responses to operative trauma, and muscle relaxation.

The concept of intravenous medical therapy arose with Percival Christopher Wren and Johann Daniel Major around 1665, the apparatus crude — quill and bladder — with controversy over priority immediately engendered. No doubt that the invention of the hollow needle and "hypodermic" syringe, mid-nineteenth century, made possible both regional and intravenous anesthesia, about 50 years after the inhalation method had proved feasible. In an unpublished essay, Sykes, author of "The First Hundred Years of Anaesthesia", nominates Pierre Cyprien Oré as the pioneer for his use of chloral hydrate intravenously. Oré's observations appeared in an 1875 Parisian volume entitled, "Etudes Cliniques sur l'Anesthésie par la Méthode des Injections de Chloral dans les Veines."

To be sure, the essential intravenous compound would be one with appropriate pharmacokinetic and pharmacodynamic properties. These qualifications were partially met by Fischer and von Mering in their synthesis of the barbiturates, around 1892, and their subsequent chemical modification by others. The picture came into focus in the 1930's with utilization of the so called short-acting intravenous barbiturates. Since that time many disparate substances have been introduced to anesthesia both as induction and maintenance agents, all falling short of the universal goal. What we need perhaps is a better understanding of the endogenous substances concerned in central neuronal inhibition, so that a synthetic congener might be used for anesthetic purposes. In this packet of reprints we have attempted to call attention to some but not all of the historical antecedents of current intravenous anesthetic practice.

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Professor of Anaesthesia
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SELECTED PAPERS ON INTRAVENOUS ANESTHESIA

1. Wren, Christopher: An account of the rise and attempts, of a way to convey liquors immediately into the mass of blood. *Philosophical Transactions of the Royal Society of London* 1: 128-130, December 4, 1665

2. Rynd, Francis: Neuralgia—Introduction of fluid to the nerve. (Reported by Mr. Richard Gregory.) *Dublin Medical Press* 13: 167-168, 1845

3. Wood, Alexander: New method of treating neuralgia by the direct application of opiates to the painful points. *Edinburgh Medical and Surgical Journal* 82: 265-281, 1855

4. Oré, Pierre-Cyprien: De l'anesthésie produite chez l'homme par les injections de chloral dans les veines. *Comptes rendus des séances de l'Académie des sciences* 78: 515-517, 651-654, 1874, (with English translation.)

5. Zerfas, LG, McCallum, JTC, Shonle, HA et al: Induction of anesthesia in man by intravenous injection of sodium iso-amyl-ethyl barbiturate. *Proceedings of the Society for Experimental Biology and Medicine* 26: 399-403, 1929

6. Weese, Hellmuth: Pharmakologie des intravenösen kurznarkotikums Evipan-Natrium. *Deutsche Medizinische Wochenschrift* 59: 47-48, Jan. 13, 1933, (with English translation.)

7. Lundy, John S: Intravenous anesthesia. Preliminary report of the use of two new thiobarbiturates. *Proceedings of the Staff Meetings of the Mayo Clinic* 10: 536-543, 1935

PHILOSOPHICAL TRANSACTIONS:

GIVING SOME

ACCOMPT

OF THE PRESENT

Undertakings, Studies, and Labours

OF THE

INGENIOUS

IN MANY

CONSIDERABLE PARTS

OF THE

WORLD.

Vol I.

For *Anno* 1665, and 1666.

In the *SAVOY*,

Printed by *T. N.* for *John Martyn* at the Bell, a little without *Temple-Bar*, and *James Allestry* in *Duck-Lane*, Printers to the *Royal Society*.

PHILOSOPHICAL TRANSACTIONS.

Munday, *Decemb.* 4. 1665.

The Contents.

An Account of the Riſe and Attempts, of a Way to convey Liquors immediately into the Maſs of Blood.

Whereas there have lately appeared in publick ſome *Books*, printed beyond the Seas, treating of the Way of *Injecting Liquors into Veins*; in which Books the *Original* of that *Invention* ſeems to be adſcribed to others, beſides him, to whom it really belongs; It will ſurely not be thought amiſs, if ſomething be ſaid, whereby the true *Inventor*'s right may beyond exception be aſſerted and preſerved; To which end, there will need no more, than barely to repreſent the *Time* when, and the place where, and among whom it was firſt ſtarted and put to tryal. To joyn all theſe circumſtances together, 'Tis notorious, that at leaſt ſix years ſince (a good while before it was heard off, that any one did pretend to have ſo much as thought of it) the Learned and Ingenious Dr. *Chriſtopher Wren* did propoſe in the Univerſity of *Oxford* (where he now is the Worthy Savilian Profeſſor of *Aſtronomy*, and where very many Curious Perſons are ready to atteſt

teſt this relation) to that Noble Benefactor to Experimental Philoſophy, Mr. *Robert Boyle*, Dr. *Wilkins*, and other deſerving Perſons, That he thought, he could eaſily contrive a Way to convey any liquid thing immediately into the Maſs of Blood; *videl.* By making Ligatures on the Veines, and then opening them on the ſide of the Legature towards the Heart, and by putting into them ſlender Syringes or Quills, faſtened to Bladders (in the manner of Glyſter-pipes) containing the matter to be injected; performing that Operation upon pretty big and lean Doggs, that the Veſſels might be large enough and eaſily acceſſible.

This Propoſition being made, M. *Boyle* ſoon gave order for an *Apparatus*, to put it to Experiment; wherin at ſeveral times, upon ſeveral Doggs, *Opium* and the Infuſion of *Crocus Matallorum* were injected into that part of the hind-legs of thoſe Animals, whence the Larger Veſſels, that carry the Blood, are moſt eaſy to be taken hold of: whereof the ſucceſs was, that the *Opium*, being ſoon circulated into the Brain, did within a ſhort time ſtupify, though not kill the Dog; but a large Doſe of the *Crocus Metallorum*, made an other Dog vomit up Life and all: All which is more amply and circumſtantially delivered by Mr. *Boyle* in his Excellent Book of the *Uſefulneſs of Experimental Philoſophy*, Part 2. Eſſay 2. pag. 53, 54, 55. Where 'tis alſo mentioned, that the fame of this Invention, and of the ſucceeding Tryals being ſpread, and particularly coming to the knowledge of a Foreign *Ambaſſadour*, that was curious, and then reſided in *London*, it was by him tryed with ſome *Crocus Metallorum*, upon a Malefactor, that was an inferiour Servant of his; with this ſucceſs, that the Fellow, as ſoon as ever the Injection began to be made, did, either really or craftily, fall into a ſwoon; whereby, being unwilling to proſecute ſo hazardous an Experiment, they deſiſted, without ſeeing any other effect of it, ſave that it was told the Ambaſſadour, that it wrought once downwards with him. Since which time, it hath been frequently practiſed both in *Oxford* and *London*; as well before the *Royal Society*, as elſewhere. And particularly that Learned

Phyſitian, Dr. *Timothy Clerke*, hath made it part of his buſineſs, to purſue thoſe Experiments with much induſtry, great accurateneſs, and conſiderable obſervations thereon; which above two years ſince, were by him produced and read before the *Royal Society*, who thereupon deſired him, as one of their Members, to compleat, what he had propoſed to himſelf upon that ſubject, and then to publiſh the ſame: the Effect whereof 'tis hoped, will now ſhortly appear, and not prove unwelcome to the Curious.

Some whereof, though they may conceive, that Liquours thus injected into Veines without preparation and digeſtion, will make odde commotions in the Blood, diſturb Nature, and cauſe ſtrange Symptoms in the Body, yet they have other thoughts of Liquors, that are prepared of ſuch things, as have paſſed the Digeſtion of the Stomach; for example, of Spirit of Urine, of Harts-horn, of Blood, *&c.* And they hope likewiſe, that beſide the *Medical* Uſes, that may be made of this *Invention*, it may alſo ſerve for *Anatomical* purpoſes, by filling, after this way, the Veſſels of an Animal as full, as they can hold, and by exceedingly diſtending them, diſcover *New* Veſſels, *&c.* But not now to enlarge upon the Uſes, the Reader may ſecurely take this Narrative, as the naked real Matter of Fact, whereby 'tis as clear, as Noon day (both from the Time, and irrefragable Teſtimony of very many conſiderable Perſons in that Univerſity, who can joyntly atteſt it; as well as from that particular unqueſtionable one of Mr. *Boyle* and his worthy Company, who were the firſt Eye-witneſſes of the Tryals made,) that to *Oxford*, and in it, to Dr. *Chriſtopher Wren*, this Invention is due; and conſequently, that all others, who diſcourſe or write of it, do either derive it from Him, or are fallen upon the ſame Deviſe ſeveral years after Him.

Publiſhed with Licence.

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for *Richard Davis*, 1665.

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MDCCCXLV.

city of Edinburgh, the Surgeons' or Chirurgeons' Craft forms one of the fourteen incorporated trades of that city, and the members or fellows of the said craft are entitled to elect a deacon of craft to represent them in the convenery of the said city; and whereas it is expedient that the connection of the surgeons with the incorporated trades, and the convenery and municipal corporation of the city, should cease; be it enacted, that if her Majesty shall be pleased to grant a new charter to the Royal College of Surgeons at Edinburgh, wherein it shall be granted that there shall no longer be a surgeons' or a chirurgeons' craft, forming one of the incorporated trades of the city of Edinburgh, then upon the grant and acceptance of the said charter to and by the said royal college, the incorporated trades of the said city shall consist of thirteen only; and it shall not be lawful for the surgeons or chirurgeons to elect a deacon of craft, or to be represented in any way in the convenery, or to have any voice in the election of deacon convener, but the deacons of the remaining thirteen incorporated trades only shall compose the convenery, and shall elect the deacon convener, and shall exercise the powers now in use to be exercised by the deacons of the fourteen incorporated trades; and all municipal privileges belonging to and now enjoyed by the members of the surgeons' or chirurgeons' craft, as one of the incorporated trades of the city, shall cease, and no person shall thenceforward be entitled to any such privileges by reason of his being or becoming a member or fellow of the body or Royal College of Surgeons of Edinburgh: provided always, that nothing herein contained shall be taken to deprive the Royal College of Surgeons of Edinburgh of any other corporate rights now enjoyed by them in virtue of any charters, statutes, letters patent, or usage not expressly repealed or altered by this act, or by any charter granted in pursuance of this act, or of the right of presentation to the Trades Maiden Hospital now enjoyed by them, or to relieve the said Royal College of Surgeons from any obligation connected with such right of presentation.

4. New charter may be granted to King's and Queen's College of Physicians in Ireland. 40 Geo. 3, c. 84 (I.)

And whereas an act was passed by the parliament of Ireland, in the fortieth year of the reign of King George the Third, intituled, "An act for repealing an act passed in the twenty-fifth year of his present Majesty, intituled, 'An act for establishing a complete School of Physic in this kingdom;' and also for repealing an act passed in the thirty-first year of his present Majesty, intituled, 'An act to explain and amend an act for establishing a complete School of Physic in this kingdom;' and also, for extending and enlarging the powers of the President and Fellows of the King and Queen's College of Physicians, and establishing a complete School of Physic in this kingdom," whereby certain provisions were made which were deemed expedient and necessary for the good government of the last-mentioned college; and whereas it is expedient that certain changes should be made in the constitution of the said college: and whereas the said college is willing that such changes should be made, but the same cannot be effected without the authority of parliament; be it enacted, that it shall be lawful for her Majesty to grant, and for the said corporation to accept, any new charter or charters for making from time to time such alterations as shall be deemed by her Majesty expedient, in the name and constitution of the said college, and that the grant and acceptance of any such new charter shall operate as a repeal of the said act of King George the Third, so far as the same shall be inconsistent with or repugnant to such new charter.

5. Charters not to contain new restrictions in the practice of physic or surgery.

Provided always, and be it enacted, that nothing herein contained shall extend to authorise her Majesty to create any new restriction in the practice of physic or surgery, or to grant to any of the said corporations or colleges any new powers or privileges, contrary to the common law of the land; and that no such new charter shall in anywise prejudice, affect or annul any of the existing statutes or bye-laws of the corporation or college to which the same shall be granted, further than shall be necessary for giving full effect to the alterations which shall be intended to be effected by such new charter and by this act in the constitution of such corporation or college.

6. Act may be amended and repealed.

And be it enacted, that this act may be amended or repealed by any act to be passed in this session of parliament.

ORIGINAL REPORTS OF MEDICAL AND SURGICAL PRACTICE.

MEATH HOSPITAL AND COUNTY OF DUBLIN INFIRMARY.

NEURALGIA—INTRODUCTION OF FLUID TO THE NERVE.

BY MR. RYND.

(Reported by Mr. Richard Gregory.)

Margaret Cox, ætat. 59, of spare habit, was admitted into hospital, May 18, 1844, complaining of acute pain over the entire of left side of face, particularly in the supra-orbital region, shooting into the eye, along the branches of the portio dura in the cheek, along the gums of both upper and lower jaw, much increased in this situation by shutting the mouth and pressing her teeth close together, and occasionally darting to the opposite side of the face and to the top and back of her head. She states that about six years ago she fell from a wall, and, in the act of falling, a stone struck her in the temple; that twelve months after this she was much exposed to cold, and one night was suddenly seized with the most agonizing pain in the situations above described. "She thought her eye was being torn out of her head," and her cheek from her face; it lasted about two hours, and then suddenly disappeared on taking a mouthful of ice. She had not had any return for three months, when it came back even worse than before, quite suddenly, one night on going out of a warm room into the cold air. On this attack she was seized with chilliness, shivering, and slight nausea; the left eye lachrymated profusely, and became red with pain; it went in darts through her whole head, face, and mouth, and the paroxysm lasted for three weeks, during which time she never slept. She was bled and blistered, and took opium for it, but without relief. It continued coming at irregular intervals, but each time generally more intense in character, until at last, weary of her existence she came to Dublin for relief.

She had been salivated three times, and had been so much in the habit of taking laudanum that latterly half a drachm, three times in the day, had no effect in lulling the pain, and was the quantity she commonly took. She was a miserable sallow-complexioned looking creature, had been sleepless for months, and her face was furrowed with constant pain.

On the 3rd of June a solution of fifteen grains of acetate of morphia, dissolved in one drachm of creosote, was introduced to the supra-orbital nerve, and along the course of the temporal, malar, and buccal nerves, by four punctures of an instrument made for the purpose. In the space of a minute all pain (except

that caused by the operation, which was very slight,) had ceased, and she slept better that night than she had done for months. After the interval of a week she had slight return of pain in the gums of both upper and under jaw. The fluid was again introduced by two punctures made in the gum of each jaw, and the pain disappeared. After this the pain did not recur, and she was detained in hospital for some weeks, during which time her health improved, her sleep was restored, and she became quite a happy looking person. She left the hospital on the 1st of August in high spirits, and promised to return if she ever felt the slightest pain again. We conclude she continues well, for we have not heard from her since.

Case II.—R. Dolon, ætat. 28, a thin spare man of middle stature, was admitted into hospital 9th September, 1844, and came under Mr. Rynd's care on the 10th of November, complaining of acute pain in the right hip, thigh, and leg, to the sole of the foot, along the entire course of the sciatic nerve and its branches, but chiefly in the main trunk of the nerve. He is unable to sleep from the pain, and quite unable to walk. He is much emaciated, and the muscles of the limb are attenuated and wasted. He has been ill for three years, during which time he has been almost always confined to bed. He has been frequently treated for the disease with calomel, to produce salivation, cupping, blistering, leeching, &c., all without any salutary effect. Exposure to cold and wet is assigned as the cause of the disease.

On the 13th of November the fluid was introduced, ten grains acetate morphiæ to the drachm of creosote, one puncture behind the trochanter, and one half-way down the thigh. He was instantly relieved from pain, and walked steadily through the ward without any pain or difficulty; before, walking increased the pain. For about half an hour after the operation he felt uneasiness from the puncture.

16th. Says he is perfectly well in the thigh, and feels only a slight pain in the course of the anterior tibial nerve. The fluid was again introduced to-day to the seat of pain by two punctures; it disappeared as before.

29th. Says he is perfectly well; has walked every day since; has slight stiffness in the knee from previous want of use.

Ordered; Camphorated oil to rub the knee with.

December 15th. Left hospital to-day, saying he felt perfectly free from all pain and uneasiness.

February 6th. He walked up to Dublin to-day, (twenty miles) and says that since the last operation, on the 16th of November, he has never felt his old pain, and is perfectly well.

ON THE

PHYSICAL AND MEDICINAL QUALITIES OF INDIAN HEMP, &c., &c.

BY M. DONOVAN, ESQ.

(From the Dublin Medical Journal.)

(Continued from No. cccxxii, page 154.)

I have now done with my own case, and shall proceed to describe the effects of this powerful medicine on other persons labouring under various kinds of painful disease.

Mr. Hanlon, watchmaker, had long laboured under violent sciatica, which confined him to bed for nine weeks. After ineffectually trying the usual remedies, Dr. Ribton directed for him twelve grains of the *weak* resinous extract (at this time it was the best procurable) in three pills, one to be taken three times that day. No good effect having been produced, he next morning took another pill, and at mid-day another. In the evening, happening to converse with a lady, he imagined there was a third person speaking to him behind his chair, and even though he turned round and saw that there was no one, he still thought he heard the voice. He felt stupid and fatigued. During the next day he took twelve grains of the extract. At night he became so overpowered with drowsiness that he could scarcely undress himself. Having got into bed, the pain, up to that time very severe, left him; he became "tranquil and happy in his mind." He soon fell asleep, and was no further affected: slept soundly until six o'clock in the morning, although his disease allowed him but three hours every other night. Next day the pain did not return until late; he was so drowsy that he was constantly obliged to walk about, but on sitting down the drowsiness returned. During this stupor the pain left him, and although it sometimes returned, it was never so severe as before.

Some months after, the same patient was attacked with a pain in his instep, unaccompanied by swelling or redness; it was constant during the day, but allowed him five or six hours' respite at night. He was put on the *strong* tincture of resinous extract of hemp, of which he took fifteen minims at ten o'clock in the morning. In two hours he became so drowsy that he was obliged to keep himself in motion lest he should fall asleep. Transactions that had occurred a few minutes before appeared to him to have happened years ago, and were recollected through a mist of memory; "when spoken to, the voice appeared to him to come through a long tube, and to be conveyed through his stomach to his ear." In taking hold of any object he felt as if something was interposed between him and his fingers. His mouth was dry, and he perceived a bitter taste in it. This condition lasted until six o'clock, when he dined with an excessive appetite.

He represents the tendency to sleep, and the efforts to resist it, as very distressing. At nine o'clock he was still so much affected that people walking in the street appeared to him to move without sound, like automatons, or in a flitting way, like enchantment. During this state he lost the true perception of time, and if he closed his eyes for a moment, he imagined that he had slept for a long period, and being aroused he forgot where he was. If not disturbed during the drowsy periods he had no pain; but on being fully awoken it returned as badly as ever.

In two nights after this he took fifteen minims of the same tincture. Within three hours he found himself "unnaturally drowsy, yet unusually hungry;" he went to bed; slept until six in the morning without any annoyance; but at one o'clock that day he had a slight return of pain, and in the evening it was as bad as ever. At night he repeated the fifteen minims, soon after was almost quite free from pain; went to bed, slept profoundly until six in the morning, got up perfectly well, and in the middle of the day became irresistibly hungry at an unusual time. For two other nights he took his dose with constantly increased benefit: and on the eighth day he was perfectly restored, and walked as well as ever.

Mr. Hanlon describes that for two months before this attack his appetite was much impaired, half a cup of tea and a small bit of bread being his breakfast. From the time of taking the second dose of tincture of hemp his allowance was tripled, with the addition of two eggs. He represents himself better in health, and more competent to all his duties than for many months before. He did not at any time feel exhilaration from the medicine. The foregoing account is given nearly in his own words, taken down by me from his dictation. During one of his attacks, while

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OF THE

LATEST AND MOST IMPORTANT DISCOVERIES

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VOLUME EIGHTY-TWO,

1855.

EDINBURGH:

ADAM AND CHARLES BLACK:

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MDCCCLV.

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No. CCIII.

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PART I.—Original Communications.

PART II.—Critical Analysis.

I have purposely refrained from noticing the spread of the disease throughout the city generally, chiefly on account of my inability to do that subject justice, and further, because we may reasonably look to the various district medical officers in connection with the different boards for the most accurate and complete information. One thing, however, I feel bound to notice, because my position as hospital physician gave me an excellent opportunity of witnessing these, namely, the excessive labours which the gentlemen to whom I have just alluded underwent. I do believe that the profession generally entertains a very inadequate idea of the duties performed by district medical officers during epidemics of cholera. I have some right to speak of the indefatigable, disinterested, and generous manner in which, during several months, the visitation of cholera patients was daily and nightly performed by the gentlemen connected with the City Parish. It is proper that the Society should have an independent testimony to the zeal with which they were always animated, the more so that one of their number,[1] and a member of this Society, in the very midst of his labours, fell a victim to the disease.

ART. IV.—*New Method of Treating Neuralgia by the direct application of Opiates to the Painful Points.* By ALEXANDER WOOD, M.D., F.R.C.P., Lecturer on Practice of Medicine.

An immense improvement was effected in our treatment of neuralgic affections, when M. Valleix directed attention to the fact, that while, on the one hand, the superficial nerves of the body are of all others the ones most commonly affected with this disease, there are some points of their course in which it is much more liable to be seated than in others, although, in these, no structural alterations can be discovered to account for this liability. These points are usually more or less morbidly sensible to pressure, even in the intervals between the attacks of the sharp lancinating intermittent pain. A very slight touch in these situations is often sufficient to excite acute suffering; in other cases, however, even firm pressure is borne without any complaint. The points

[1] Dr John Mackay, in whom, to a most amiable character and an excellent knowledge of his profession, was added an enthusiastic desire to dispense its benefits to the suffering poor, and who, by reason of his unwearied labours, there is too much reason to fear, fell an easy prey to cholera.

in the course of any nerve which are thus liable to be the seat of tenderness are, according to Valleix:—

1. The place of emergence of the nervous trunk.
2. The point where a nervous twig traverses the muscles to ramify on the integuments.
3. The point where the terminal branches of a nerve expand in the integuments.
4. The point where nervous trunks become superficial during their course.

It is perhaps scarcely necessary to remark that all these points are precisely those where the nerve tends towards the surface, and therefore where, of course, it is the most amenable to local treatment.

Acting on the result of this observation, M. Valleix introduced a plan of treatment, which, as an external remedy, I have largely employed ever since my attention was first directed to his work in 1842.

It consists in the application of a succession of small blisters *over the points* in the course of the nerves which are painful on pressure. Valleix does not recommend, as a general rule, the application of morphia endermically, but suggests that it may be attempted with advantage in some cases. I have almost invariably employed an ointment containing morphia to dress the blistered surface, and have been accustomed to ascribe much of the benefit of the treatment to this. In some cases, I have seen relief follow the application of an ointment containing strychnine to the blistered surface, but this must be used with great caution, as very disagreeable results often ensue from its use.

It has frequently occurred to me, however, that a more direct application of the narcotic to the affected nerve, or to its immediate neighbourhood, would be attended with corresponding advantage, and as the painful points so frequently correspond with those in which the nerve becomes superficial, I thought this might perhaps be accomplished. In pursuit of this object, I have made several attempts to introduce morphia directly by means of acupuncture needles and otherwise, but without success.

Having occasion, however, about the end of 1853, to endeavour to remove a nævus by injection with the acid solution of perchloride of iron, I procured one of the elegant little syringes, constructed for this purpose by Mr Ferguson of Giltspur Street, London. While using this instrument for the nævus, it occurred to me that it might supply the means of bringing some narcotic to bear more directly than I had hitherto been able to accomplish on the affected nerve in

neuralgia. I resolved to make the attempt, and did not long lack opportunity.

Miss ——, an old lady, who had long laboured under gastric and nervous symptoms, had suffered severely for four days from cervico-brachial neuralgia. This lady had the idiosyncrasy of not being able to take opium. Of this she had warned me many years before, when she first came under my care, and I consequently never prescribed it for her; however, once, when she was seen with me by the late Dr J. H. Davidson, he, disbelieving her former experience, prescribed opium, with the effect of bringing on a severe fainting fit.

The narration of her case may date from November 26th. She had not been able to sleep for the three previous nights from the violence of the neuralgic pain, and was quite exhausted with severe suffering. The usual internal remedies, with the exception of opium, had been tried, but without the least alleviation of her agony. Under these circumstances, I resolved to put in practice the plan which I had so long revolved in my mind.

Accordingly, on November 28th, I visited her at 10 P.M. to give the opiate the benefit of the night. Having ascertained that the most tender spot was the post clavicular point of Valleix, I inserted the syringe within the angle formed by the clavicle and acromion, and injected twenty drops of a solution of muriate of morphia, of a strength about double that of the officinal preparation.

In about ten minutes after the withdrawal of the syringe the patient began to complain of giddiness and confusion of ideas; in half an hour the pain had subsided, and I left her in the anticipation of a refreshing sleep.

I visited her again about 11 A.M. on the 29th; was a little annoyed to find that she had never wakened; the breathing also was somewhat deep, and she was roused with difficulty. Under the use of somewhat energetic stimuli, however, these symptoms disappeared, and from that time to this the neuralgia has not returned.

CASE II.—Mrs ——, aged 30, of a gouty family, four years married, no family, short, and plump habit, very pale, menstruation scanty and painful, countenance anxious, urine high coloured, suffers much from flatulence and indigestion, tongue loaded, pulse 98.

After exposure to cold and damp, was seized with shivering and pain in the loins on the 9th December 1853. I saw her on the 13th. The pain in the back had then subsided, but the whole region of the left hip was tender, a distinct painful point was felt near the posterior superior spinous pro-

cess of the ilium, and another farther down, about the middle of the thigh.

Twelve leeches were directed to be applied as nearly as possible in the course of the sciatic nerve, their use to be assiduously followed by that of warm fomentations, and one of the following powders to be taken every sixth hour.

℞ Pulv. Doveri, gr. v.
Pulv. Colchici, gr. iv.
Hydrarg. c. creta, gr. ii.
M. Ft. pulv.

Next day (14th December) she was considerably relieved; had enjoyed a short but refreshing sleep; the bowels had acted three times freely, the motions being very dark and offensive; thought herself much weakened by the bleeding and purging; directed to continue the powders.

December 15.—Tongue cleaner, gums swollen and spongy, coppery taste in mouth, tenderness of hip gone, the pain otherwise much the same as on the preceding day; feels sleepless and uncomfortable; bowels have not again acted.

Stop the powders; take two turpentine capsules three times a-day; drink plentifully of linseed tea with gum dissolved in it.

December 16.—Feels very uncomfortable, the turpentine has produced severe dysuria, pulse 104, tongue coated, the pain in the hip has not returned, but the pains are more severe and lancinating in the middle of the thigh and round the head of the fibula.

The syringe was introduced at the painful spot in the middle of the thigh, and 10 drops of Battley's sedative solution were injected without any perceptible effect but that of slight smarting at the seat of the puncture. Two hours afterwards the pain ceased, and the patient fell into a deep sleep, from which she woke entirely free from pain in the thigh or leg, but suffering slightly in the region of the malleolus externus.

December 18.—The pain in the malleolus is very severe, and is much aggravated by pressure; the pain in the hip and thigh is entirely gone.

The injection repeated in the malleolar region. This operation was followed by no perceptible effect; but in about four hours the pain began to abate, and ceased altogether in about eight hours from the injection.

The state of the patient's general health required some attention; she is now much better, and her sufferings at the menstrual period are diminished, but she has had two slight

returns of the sciatica, for which, at her own request, she has been treated by the opiate injections.

CASE III.—Mrs ——, æt. about 50, widow, plethoric habits, hysterical temperament, has suffered since the cessation of the menstrual flux about 10 years ago, from various anomalous symptoms, of a nervous kind, indicating great spinal irritation. Her liver is enlarged, and her heart is often functionally disordered. She has had severe attacks at different times of visceralgia, and has often suffered from neuralgia, chiefly of the dorso-intercostal and lumbo-abdominal varieties. Her very full habit, as also the cause from which these symptoms obviously arose, coupled with the evidence of cerebral congestion, with which her attacks were frequently accompanied, as also the fact of her pulse being at these times full and firm, her skin hot, and her urine high-coloured, had led me to treat them by cupping, purging, antimonials and salines. Opiates had no effect in alleviating her sufferings, and belladonna and aconite affected too powerfully her nervous system without abating her suffering.

I first tried the syringe with her on the 19th of April 1854, when she was suffering from a severe attack of lumbo-abdominal neuralgia.

The syringe was inserted in the *lumbar point*, a little to the outside of the vertebræ, and 25 drops of Battley's solution were injected.

She had an easier night, and the pain, though somewhat better next morning, was by no means removed, and the following day it returned with such severity that her former treatment had to be resorted to with decided relief. She has certainly suffered less since the operation.

CASE IV.—A married female, aged 23, in the lower rank of life, consulted me May 2, 1854. Had suffered three months previously from a miscarriage which had weakened her much; her countenance is exsanguine, lips nearly colourless, tongue and gums white. A loud bruit is audible over the heart and in the carotids. Has also had a great deal of mental distress.

About three weeks ago came from the country on the outside of a coach, and sat on a very damp cushion. Next day felt as if one leg was longer than the other; she had much pain in the lower part of the abdomen, in which she thought she felt a large painful ball. Pressure on the spinous processes of her dorsal vertebræ gives no pain; but a painful spot is distinctly to be detected a little to the left side. Os uteri open and flabby, very tender on pressure; surface velvety, much mucous discharge.

The following medicine was ordered, with nourishing food:

R Citratis Ferri ʒii.
Syrupi ʒss.
Aquæ cassiæ ʒ v. ss.
m
Sumat coch., amp. ter. indies.

May 16.—Somewhat improved in appearance, pain not abated; 25 drops of Battley's solution were injected into the painful point. About an hour afterwards was seized with violent vomiting, with shivering and severe constitutional disturbance; pain not abated.

May 17.—Vomiting has ceased, but returns with every attempt to swallow, pain much worse, no sleep, tongue loaded, bowels costive. Ordered to use ice freely, and to take a drop of Fleming's tincture of aconite every third hour for four times.

May 18.—Stomach much better, but the pain in the back is not abated. Ordered friction with the Tinctura saponis c. opio.

May 19.—Pain which was easier during the day, became much more severe at night, and she had an opiate by the advice of a friend. Severe vomiting followed its use, and it had no effect either in allaying the pain or in procuring sleep. I recommended her to persevere with the iron for some time, but have lost sight of her.

Case V.—Mr ———, after much exposure to wet, consulted me on the 4th June 1854, on account of a severe attack of sciatica. I prescribed a smart dose of calomel and rhubarb, to be followed by an antimonial mixture, and on the evening of the following day, injected twenty drops of Battley's sedative solution. Four hours afterwards he fell into a deep sleep, and wakened free from pain.

Case VI.—Miss ———, æt. about fifty, very stout, consulted me some years ago, about a uterine affection, accompanied with severe lumbo-abdominal neuralgia. The pain she suffered was great, and the lameness it occasioned entirely precluded the possibility of walking. I directed attention, in the first instance, to the uterine symptoms, hoping that on their removal, the neuralgia would disappear spontaneously. In this, however, I was disappointed. Great benefit undoubtedly followed the relief of the internal disorder, and the lameness diminished perceptibly; still the pain evinced little or no disposition to abate. On the 2d June 1854, I inserted thirty drops of Battley's solution. Severe vomiting followed, and the pain was entirely diminished.

From that date, I directed my attention chiefly to the constitutional treatment, until the increased severity of the pain drew my attention to it. I injected thirty drops of Battley on the left side on the 13th December 1854.

December 14.—Pain on left side nearly gone; that on right very bad.

December 16.—Repeat the injection on the right side.

December 17.—Pain much relieved.

I saw this lady again on the 29th December The pain was much easier, but she still continued lame, and the pain was apt to increase after any exertion.

CASE VII.—A gardener, advanced in life, after exposure to cold and wet, was seized on the 18th November with severe lumbago. This had yielded by the 2d December to the usual treatment; but there remained after its disappearance symptoms of that very rare form of neuralgia described by Cotungo and subsequently by Chaussier, and denominated by Valleix crural neuralgia.

He says he has lost the power of his limbs, though this is obviously not the case.

There is a painful point in the loins, another still more marked in the groin, a third at the head of the fibula, a fourth on the dorsum of the foot.

December 12.—15 drops of Battley's solution were injected into the painful point on the loins. Next day the patient reported that he had felt no peculiar effect except that the pain was entirely gone from every point but the knee.

CASE VIII.—Mrs ——, aged about 80, has been suffering for some time from severe pain in the chest, cough, with mucous expectoration, which, together with the cough, have prevented her from sleeping for some nights. She is extremely deaf, so that it is not easy to make out her symptoms. I visited her first on the 12th December 1854. The bronchitic symptoms were then so severe that I directed attention exclusively to them. I need not detail the treatment which has no bearing on the matter on hand. On the 21st, I found the cough nearly gone, but she was still sleepless from the pain of the back, which I then for the first time examined. A painful spot was soon pointed out by the patient herself, seated near the trochanter. The integuments here were deeply seamed and scarred; the result she informed me of deep incisions made when she laboured under what she called "white swelled leg" (phlegmasia dolens I presume), 54 years before. Into this point I injected 30 drops of Battley. Next day (22d Dec.), when I visited her, she told

me she had enjoyed a capital sleep; but what was that you gave me, she added, I saw the most glorious visions all night. Since then the lancinating pain has ceased, though what she describes as a dull stounding pain remains.

CASE IX.—Miss ——, aged about 30. About twelve years ago, while travelling on the continent, suffered from severe influenza; while scarcely convalescent, by the breaking down of a bridge, was precipitated into a river, and had to sit some hours in a carriage with wet clothes. After this suffered from constant aching in the back, which rendered the supine position essential. Some amelioration of this took place under medical treatment. Her menstruation became scanty and painful; for this she consulted Dr Simpson, and was relieved by his treatment. Since then has had attacks of pain in back at intervals.

Last spring, pain in back became severe, extending down to knee—was recommended to take aconite, which she found to give relief. Her left side is constantly cold. When in the country, her medical attendant scarified the back and rubbed in morphia. This was done nineteen times, and she obtained some relief, but the operation was very painful.

December 24.—The pain was brought on by exertion to-day, but is not very severe. 25 drops were injected—She passed a very restless uneasy night, with much vomiting; pain in back gone.

Dec. 26.—Slight return of pain; but on the whole better. I have heard since that this young lady's health is permanently improved.

For the following cases I am indebted to Dr Thomas Wright, F.R.C.P., by whom the remedy was tried on my suggestion:—

Dr Wright's two cases treated by Dr Wood's method.

1. Mary Ann Forester applied at the New Town Dispensary on account of a painful affection of the ulnar nerve and its branches in the arm, fore-arm, and hand. During the late severe frost she had been discharged from the Infirmary cured of necrosis of the lower half of the humerus, and had afterwards been much exposed to cold, having frequently been obliged to sleep in a common stair. The limb, in consequence thereof, became severely painful, especially at night, and prevented her from either sleeping or following any occupation. She complained of occasional rigors, and there was considerable tenderness over the injured part of the

bone, but the pulse was natural and the tongue clean. Forty drops of Battley's solution were injected into the cellular tissue above the inner condyle, the limb was rolled in flannel and bandaged, she was put upon a course of alterative and aperient medicine, and ordered to visit me again in two days. Directly after the injection of the opiate the skin over, and for two or three inches round, the part became erythematous and covered with white patches of urticaria; but the severe pain in the fore-arm and hand immediately ceased. At her next visit she stated that there had been no return of the pain, but that she had suffered much from vomiting and headache, which came on directly after the injection, and lasted all the next day. She visited me only once afterwards, at which time the pain had not returned, but she had still much tenderness over the diseased bone, and occasional rigors. She was able to carry a basket of vegetables for sale.

2. Mrs A. B., a widow lady, aged 52, has been subject to periodic headache for several years. The attacks recur every fortnight or three weeks, and commence with pain in the nerves of the integument at the external angle of the right orbit and in the posterior branch of the second cervical nerve of the right side. After from four to six hours, during which time the nerves of all the right side of the scalp become severely affected, the pain either ceases altogether or passes to the other side of the head, and runs a similar course. At the commencement of a later attack, the injection of twenty drops of Battley's solution into the cellular tissue around each of the starting points of pain before mentioned was attended with entire relief for several hours, after the expiration of which the pain commenced on the other side of the head, and was attended with more than usual suffering on account of the constitutional effects caused by the opiate.

I have tried this mode of using narcotics on some other cases not so appropriate. I am quite satisfied that in those not unfrequent cases where the disease has a central, not a centripetal origin, it is quite useless, unless from the power which it may for the time exercise on the imagination.

In one case in which I tried it, by the kind permission of Dr John Brown, the puncture was, in a few minutes, surrounded by a blush of urticaria.

In considering the *modus operandi* of this new application of remedial means, I think the following propositions will guide us to a right conclusion :—

§ 1. Medicines when exhibited have usually two effects—

1*st*, *The local or topical*—the particular effect of the medicine on the tissue to which it is applied; 2*d*, *The remote effects*—being physical, chemical, or vital changes produced on parts at a distance from those to which the medicine is directly applied, or on the system at large.

§ 2. The manner in which the local effect is produced is comparatively simple, and depends on the relation of the medicine to the tissue to which it is applied. Thus, some applications simply stimulate or irritate the tissue, the effect varying from the least powerful, which merely redden, to the strongest, which produce ulceration, or even gangrene. Others, again, form compounds with the elements of the tissue, thus chemically decomposing or corroding it, while a third class, according to Dr Christison,[1] "neither corrode nor irritate, but *make a peculiar impression on the sentient extremities of the nerves, unaccompanied by any visible change of structure.*"

§ 3. With regard to the manner in which the remote effects are produced, considerable difference of opinion prevails. Magendie[2] and his supporters contended strongly that they were conveyed by absorption from the part to which they are first applied, while Messrs Morgan and Addison[3] are of opinion that the remote effects are exclusively due to sympathy, or an impression transmitted through the nerves.

§ 4. Sir Benjamin Brodie,[4] Dr Christison,[5] and others, however, unable to adopt either view exclusively, have contented themselves with admitting this double mode of operation; "a conclusion" which Messrs Morgan and Addison agree "that all fair analogy forbids."

§ 5. With the exception of Morgan and Addison, who deny the doctrine of absorption only because they strongly hold that of sympathy, and because they think it "contrary to nature's rule to adopt two ways of attaining the same end," all authors agree in admitting absorption to be the most usual channel by means of which medicinal agents are conveyed from the part to which they are directly applied, so as to effect remote organs, or the system at large.

§ 6. Since the experiments of Hering, and more recently those of Mr Blake,[6] have shown the extreme rapidity with which the round of the circulation may be accomplished, the

[1] Treatise on Poisons, p. 1.
[2] Magendie, Annales de Chimie et de Physique.
[3] Essay on the Operation of Poisonous Agents, &c.
[4] Phil. Trans. 1811–12. [5] Treatise on Poisons.
[6] See this Journal, vols. liii. and lvi.

tendency has been greater to ascribe to absorption even those very rapid, or almost instantaneous general operations of certain poisons locally applied, which were formerly regarded as the strongest arguments for the theory of nervous transmission.

§ 7. Of the great effect of absorption we will be still more convinced, if we call to mind the rapid disappearance of the agent from the part to which it was applied,[1] coupled with its speedy detection in parts at a distance,[2] and the no less speedy communication of its qualities to the animal solids and fluids.[3] The arrest of the action of the poison by arrest of the circulation from the part,[4] and the failure of all attempts to arrest the production of remote effects by intercepting the nervous communication.[5]

§ 8. The chief agents by which absorption is effected are the veins, though the lacteals and absorbents take up certain agents, but their operation is both limited and slow.

§ 9. Different tissues vary in their absorbent power. Thus, according to the very interesting experiments of M. Vernière,[6] the mucous membrane of the intestinal canal absorbs less rapidly than the serous membranes, and they, in their turn, are less powerful channels of absorption than a vein or an open wound.

§ 10. Difference of tissue is therefore found to modify, to a great extent, the action of remedies. Thus, the stomach and intestines, which are the tissues to which medicines are generally applied, possess a considerable power of absorption, as indeed their office would lead us to suppose; nevertheless we find, from the experiments of Christison and Coindet,[7] "that when oxalic acid is introduced under the same colla-

[1] Of four ounces of solution of oxalic acid, injected by Drs Christison and Coindet into the peritoneum of a cat, and which proved fatal in fourteen minutes, though none escaped by the wound, scarcely a thirty-second part was found after death.—(See this Journal, vol. xix. 335.)

[2] As in the urine, see the very full experiments of Wöhler and Stehberger (Zeitschrift für Physiologie, Bd. für 1824–5.) Or, as in a case quoted from Fricke by Pereira (vol. i., p. 106), where iodine was detected in the tears by the formation of iodide of mercury, when calomel was applied to the eye of a patient who had been taking iodide of potassium. In the blood and chyle, as by the experiments of Tiedemann and Gmelin.

[3] Almost all the minerals, and many other substances which are given medicinally, have been detected in the bones, brain, skin, and liver (Pereira, op. cit., p. 104.)

[4] See the experiments of Ségalas, Emmert, and Blake (Muller's Physiology, and op. cit.)

[5] See the experiments of Magendie and Delille (Physiology by Milligan, p. 284.)

[6] Journal des Progres, 1827.

[7] See this Journal, vol. xix., p. 330, and Christison on Poisons, p. 29.

teral circumstances into the stomach of one dog and the peritoneum of another, the dose may be so apportioned that the same dose which does not prove fatal to the former kills the latter in fourteen minutes."

§ 11. The few experiments which we had, until very recent times, regarding the power of the pulmonary membrane to absorb poisons, tended to cause it to be regarded as a channel of extreme power. The rapidity of the fatal results which follow gaseous poisoning may be instanced, as also the experiment of M. Ségalas, who found that half a grain of solution of extract of nux vomica injected into the windpipe proved fatal, while two grains might be injected into the stomach, peritoneum, or chest, without any fatal effect.

§ 12. The experiments of Professor Simpson on the inhalation of chloroform, oil of juniper, ergotine, and other medicinal agents, also show the value of this channel for the introduction of certain medicaments into the system.

§ 13. The skin, which has at various times been employed as a medium for the introduction of medicines into the system, would appear to possess no very active power of absorption, at least unless it be denuded of its cuticle. "Accordingly," says Dr Christison,[1] "many active poisons are quite inert when applied to the unbroken skin, or even to the skin deprived of the cuticle. Hydrocyanic acid, perhaps the most subtle of all poisons, was found by Coullon to have no effect when dropped on the skin of a dog." On the other hand, Dr Madden, in his work on Cutaneous Absorption,[2] has shown, from carefully conducted experiments, the power which the healthy skin possesses of absorbing from a gaseous and from an aqueous medium, and has collected from various authors proofs of its power to absorb medicinal substances.

§ 14. Both solids and fluids have been thus absorbed by the skin. Kellie found salivation follow the use of a mercurial plaster. Arsenic employed to destroy lice has been known to produce violent inflammation. Salivation has been produced by the absorption of a solution of corrosive sublimate. Dr Madden, after immersing his hands in a solution of hydriodate of potass, detected iodine in his urine, and he also succeeded in purging himself, by applying to his skin infusions of rhubarb, jalap, and gamboge.

§ 15. There is no more rapid way of securing the action of poisons than by introducing them into a divided vein, or into several divided veins, by means of an open wound.

[1] On Poisons, p. 28.

[2] An Experimental Enquiry into the Physiology of Cutaneous Absorption, by W. H. Madden, M.D. Edin., 1838.

"Some," says Dr Christison, "which act very slowly through the stomach cause instant death when injected into a vein."

§ 16. With regard to the cellular tissue, Dr Christison states, "that it is a ready medium for introducing poisons into the blood, especially if an artificial cavity be made where the tissue is loose, but that its power as a medium of absorption has not been, and cannot easily be ascertained. On the one hand, it is difficult to apply poisons to it without also applying them to the mouths of divided vessels, and, on the other hand, it is difficult to make a set of experiments for comparison with others on the stomach, pleura or peritoneum, as the cellular tissue does not form an expanded cavity, and, consequently, the extent of surface to which a poison is applied cannot be made the same in each experiment of a series." [1]

§ 17. The experiments which approach the most nearly to direct injection of the cellular tissue are those detailed by Sir Benjamin Brodie in the Philosophical Transactions for 1811–12, in which various poisons were introduced into wounds, and were found to produce very speedy results; but in all these cases the great division of parts exposed so many blood-vessels that it is not easy to say how much of the effect was due to the cellular tissue, and how much to the action of the divided vessels.

§ 18. I am at present engaged in some experiments on this subject, in which, by means of an improved apparatus, various substances have been introduced into the cellular tissue with comparatively little injury to the adjacent vessels, and, as far as these have gone, they would lead to our ascribing great absorbent power to the cellular tissue.

§ 19. The result of what has been stated proves satisfactorily,—

1st, That medicines are more rapidly absorbed by some tissues than by others.

2d, That the stomach is by no means the most rapid way of introducing medicines into the system.

3d, That the cellular tissue has a great power of absorption.

§ 20. It has been further shown by Dr Christison, that the whole amount of difference is not to be explained by the rapidity with which absorption goes on, but is to be ascribed in part to the poison being more liable to decomposition in one tissue than in another. Thus, many remedies are much changed in the stomach, where the powers of assimilation are very strong, and the action of absorption slow.

[1] On Poisons, page 30.

§ 21. We are thus conducted to this point of the enquiry. Have we no means of introducing medicinal agents very rapidly into the body, in a situation where they will not be readily decomposed, and where, in certain cases, we can secure at once their local and their remote effects.

§ 22. The value of such a method of procedure, in many diseases, will be apparent. We shall instance but one—neuralgia.

§ 23. In neuralgia we have usually a general and a local affection, a morbid state of the system, arising from many causes, displaying various symptoms, requiring varied treatment, and existing in states of the body the most opposite; a local affection, occurring in paroxysms of violent pain, either regular or irregular, plunging like electric shocks along the course of the affected nerve, ceasing, either to be suspended for a time, or immediately to recur with still more unbearable violence.

§ 24. An affection presenting characters such as have been described, would appear to demand at once a local and a general treatment;—a local treatment directed to, and intended to mitigate the fearful anguish, under which the patient is well-nigh driven to despair; a general treatment intended to correct the "*habitus neuralgicus*" on which it depends, and having reference to the causes from which it has arisen, the state of the system in which it exists, and the diseases with which it may be associated.

§ 25. There are other circumstances in the history of neuralgia which seem to point at, and to give peculiar facilities to local treatment. It is admitted on all hands that the *superficial* nerves are of all others the most liable to the disease. It has further been shown by M. Valleix[1] that some points in the course of the nerve are more liable to be affected than others, and that these points are frequently the very ones where the nerve is most superficial.

§ 26. Further, these points can almost always be detected in the course of the disease from their extreme tenderness on pressure. Even in the intervals between the paroxysms, very slight pressure on these points is sufficient in many cases to excite severe suffering, although, in some exceptional cases, firm pressure may be applied without exciting any complaint.

§ 27. The plan of local treatment which M. Valleix proposed was the application of a succession of small blisters

[1] Traité des Néuralgies, ou Affections Douloureuses des Nerfs. Par F. L. S. Valleix. Paris, 1841.

over the points in the course of the nerves which are painful on pressure, and in all his cases it seemed to alleviate the symptoms.

§ 28. The plan of blistering is not new, but for the application of it to the tender points we are indebted to M. Valleix, and that author has effected an immense improvement in practice by showing where our local treatment, whatever that may be, ought to be applied.

§ 29. Our own experience has not confirmed the value of simple blisters, and we prefer following them up by the endermic application of morphia.

§ 30. Two strong objections, however, apply to blistering, or the endermic application of narcotics in this disease—

1st, The painful nature of the remedy.

2d, The mark which it often leaves, which is very objectionable when the disease is seated in the nerves of the face.

§ 31. Various methods of applying narcotic or other remedies more directly to the seat of the disease have been introduced. Thus we have—

1st, The *enepidermic method*, in which the agent is simply applied to the surface of the skin.

2d, The *Iatraleptic*, in which the absorbents are stimulated by friction to take up the agents which are presented to them in solution or in a minute state of division.

3d, The *endermic* proposed by MM. Lembert and Lesieur, in which the obstacle which the epidermis offers to the entrance of the remedy is overcome by previously removing it.

4th, *Inoculation*, which, largely practised for the introduction of small-pox and cow-pox into the system, has been proposed by M. Lafargue St Emilion, to be extended so as to secure the application of remedies. This method was brought before the Westminster Medical Society in February 1837, by Dr Bureaud, but from the account given in the 'Lancet,'[1] he does not seem to have been very successful, as only a slight local effect was produced. A report was made by M. Martin Solon for the Academy of Medicine,[2] on this method of inoculation by morphia, proposed by Dr Lafargue, which report comes to the somewhat damaging conclusion that the effect produced was very much the same, whatever agent was inoculated even when the experiments were made with agents as dissimilar as belladonna, strychnine, the gastric juice, chyme.

[1] Lancet, 1837, p. 826.

[2] Bullet. de l'Acad. Roy. de Med. 1836, vii., Nos. 1 and 7.

§ 32. From all this it is plain that we are still in want of a method of directly applying sedatives to the affected part, and that could such a method be suggested its value would be enhanced, could this be done almost without pain, and in a manner calculated, at the same time, powerfully and rapidly, to affect the general system.

§ 33. Of the value of such an application locally to the nerve affected, no one can be in doubt who calls to mind the result of the experiments instituted by Müller, which clearly shows that, to quote his own words, "narcotic poisons," when applied locally to nerves, have only a local effect. I held the nerve of a frog's leg which was separated from the body in a watery solution of opium, for a short time, and that portion of the nerve lost its irritability, but below the part that the poison had touched the nerve still retained this function; *opium, therefore, produces* a change in the nervous matter itself, but the influence is local.[1]

§ 34. Again, every one who has seen much of neuralgia is aware that, on the one hand, the pain, acute and agonising as it is generally, subsides spontaneously after some time; that on the other, opiates administered through the ordinary channels are usually some hours in taking effect, so that, if this class of remedies are to be of use at all, it must be an immense advantage to secure—

1st, A local effect, applied *directly* to the affected nerve.

2d, A remote effect, ensuing almost *instantaneously* on the application of the remedial agent.

§ 35. Several of the cases which I have detailed show with what rapidity narcotics take effect when introduced in this way; and in a case in which I tried it in the Royal Infirmary, through the kindness of my friend Dr W. T. Gairdner, the man, who was not at all aware of what was doing, told us that he felt as if he was drunk within a very few minutes after the introduction of the narcotic.

§ 36. These are the advantages which this new method of treatment seem to offer, and on which we venture to recommend it for trial; and I think we may safely arrive at the following important conclusions regarding it from the cases which I have submitted—

1st, That narcotics injected into the neighbourhead of the painful point of a nerve affected with neuralgia, will diminish the sensibility of that nerve, and in proportion diminish or remove pain.

2d, That the effect of narcotics so applied are not confined

[1] "Physiology," by Baly, vol. i., p. 246.

to their local action, but that they reach the brain through the venous circulation, and there produce their remote effects.

3d, That in all probability what is true in regard to narcotics would be found to be equally true in regard to other classes of remedies.

4th, That the small syringe affords a safe, easy, and almost painless method of exhibition.

5th, That, destitute as we are of any precise experiments as to the applicability of cellular tissue as a medium for the reception of medicinal agents, the experiments made with the syringe show that it seems to offer an excellent surface for the absorbent action of the venous system.

6th, That the method now detailed seems as extensively applicable as any of the methods of applying remedies to the skin, whether

Enepidermic,
Iatraleptic,
Endermic, or by
Inoculation.

ART. V.—*Brief Memorial of the Life and Writings of the late Richard James Mackenzie, M.D., F.R.C.S.*

Though departing from our usual practice, we should be doing violence to our own feelings were we not to offer a tribute of respect to the memory of one whose character, professional and private, the incidents of whose life and death, and whose intimate connection with ourselves in conducting this Journal, alike demand it.

Richard James Mackenzie, the fourth son of the late Richard Mackenzie, Esquire of Dolphinton, and deputy-keeper of Her Majesty's Signet, was born in Edinburgh on the 31st of March 1821. His early education was, in the first instance, conducted by Mr White, long eminent as a teacher of English in this city, and thereafter in the New Academy, which he entered in 1829, and where he continued uninterruptedly during the full curriculum of seven years. After leaving the Academy, where he distinguished himself, and was successful in obtaining several prizes, he received instruction from a private tutor, along with his early friend and future fellow-student in medicine, Walter Dickson, till entering upon his professional studies in the autumn of 1837. With Mackenzie the choice of medicine as a profession was no sudden determination; on the contrary, from his boyhood

COMPTES RENDUS

DES SÉANCES

DE L'ACADÉMIE DES SCIENCES.

SEANCE DU LUNDI 16 FEVRIER 1874.

PRÉSIDENCE DE M. BERTRAND.

PHYSIOLOGIE PATHOLOGIQUE. — *De l'anesthésie produite chez l'homme par les injections de chloral dans les veines.* Note de M. ORÉ, présentée par M. Bouillaud.

« Dans une Note adressée, le 29 mai 1872, à la Société de Chirurgie de Paris je disais :

« Des expériences nombreuses, variées, fréquemment répétées m'ont appris que le chloral *injecté dans les veines* constitue *le plus puissant de tous les anesthésiques;* il suffit alors de 2, 3, 4, 6 grammes de chloral, suivant le poids de l'animal, pour le plonger immédiatement dans un état d'insensibilité, qu'aucun excitant, *à part les courants électriques*, n'est capable de faire cesser. Cette insensibilité qui ressemble à celle du cadavre, dure pendant une, deux, trois, cinq heures; et, alors que les fonctions de l'axe cérébro-spinal sont momentanément anéanties, au double point de vue de la sensibilité et de la motilité, la respiration continue calme et régulière. Il est pour moi expérimentalement démontré aujourd'hui que le choral, administré par la méthode de l'injection dans les veines, *est un anesthésique chirurgical bien supérieur au chloroforme*, d'abord parce que l'insensibilité qu'il produit est infiniment plus complète et plus longue, ensuite parce qu'il ne détermine du côté du bulbe aucun de ces phénomènes asphyxiques inquiétants qui s'observent si souvent à la suite du chloroforme. »

» Les expériences sur lesquelles reposent les précédentes assertions ont été rapportées avec soin dans le Mémoire que j'ai soumis au jugement de l'Académie. Restait à vérifier si l'expérience, transportée de l'animal à l'homme, amènerait le même résultat : le fait suivant ne laissera, je l'espère, aucun doute à cet égard.

» J'ai reçu dans mon service à l'hôpital Saint-André de Bordeaux (salle 10, lit 14) un homme de 52 ans, qui, à la suite *d'un léger écrasement de l'extrémité du médius gauche*, a vu survenir de la contracture des muscles masticateurs, suivie bientôt d'un tétanos traumatique confirmé.

» A son entrée à l'hôpital, le trismus était très-marqué, l'écartement des mâchoires ne dépassait pas 5 millimètres, les muscles de la nuque et du cou fortement contracturés ne permettaient aucun mouvement dans cette région, la tête était renversée en arrière. Les membres, le tronc même, possédaient encore une certaine liberté dans leur jeu physiologique, quand le malade était en repos; mais le moindre effort pour se mouvoir, pour parler, pour avaler, amenait brusquement des contractions généralisées à tout le système musculaire. En même temps survenaient des troubles respiratoires et circulatoires se traduisant par une exagération dans la vitesse du pouls, de la dyspnée, une cyanose incomplète. Les facultés intellectuelles étaient intactes.

» L'extrémité du doigt médius gauche présentait, avec une légère contusion, une ecchymose sous-unguéale. *La moindre pression en ce point déterminait immédiatement une exagération dans la roideur tétanique et des douleurs intolérables.*

» En présence de cet état, je n'hésitai pas un instant à recourir à l'emploi du *chloral en injection intra-veineuse.*

» Le 9 février, à 5 heures du soir, j'injectai deux fois, à trois ou quatre minutes de distance, dans une des veines radiales droites, une solution de 9 grammes d'hydrate de chloral dans 10 grammes d'eau.

» Immédiatement après la seconde injection, le malade tombait dans un sommeil tranquille : la respiration, d'abord accélérée, devenait calme et régulière. Le pouls qui, avant l'injection, marquait 90 pulsations, descendait à 70; la roideur musculaire disparaissait presque complétement; les mâchoires s'écartaient de 3 centimètres et donnaient passage à la langue.

» Le passage des doigts sur la surface cutanée, les mouvements même qu'on imprimait aux membres ne déterminaient plus de convulsions réflexes. On pouvait pincer impunément le malade, sans provoquer chez lui le moindre signe de sensibilité.

» L'anesthésie était si complète que j'ai pu explorer à mon gré le doigt écrasé, alors qu'avant l'injection la moindre pression y occasionnait les douleurs les plus vives. Pensant que si je régularisais cette situation, je pourrais peut-être écarter la cause des phénomènes tétaniques, je me décidai à faire l'*avulsion* de l'ongle. J'introduisis sous lui la pointe d'une paire de ciseaux que je fis filer d'avant en arrière. Il fut ainsi divisé en deux moitiés que j'arrachai successivement avec des pinces. Cela fait, avec la pointe d'un bistouri je donnai à la plaie une netteté qu'elle n'avait pas. Pendant tout le temps que dura cette opération, *ordinairement si douloureuse,* le ma-

lade ne proféra pas les plus légères plaintes, ne fit pas le moindre mouvement.

» J'ai revu le malade à 9 heures du soir : il dormait profondément, l'anesthésie durait encore. J'ai pu, sans le réveiller, le pincer avec force sur les membres inférieurs, sur la joue, *promener la palpe de mon index sur la conjonctive oculaire, sans déterminer le moindre mouvement réflexe.* Or il est démontré aujourd'hui que, à la suite des inhalations de chloroforme, quand ce dernier phénomène se produit, la sensibilité est absolument éteinte.

» Le malade ne s'est réveillé qu'à 4 heures du matin; je ne l'ai revu qu'à 9 heures. La sensibilité était revenue, bien qu'elle fût encore incomplète, aux membres inférieurs surtout.

» Le 10 février, à 5^h30^m du soir, je fis une deuxième injection de 10 grammes de chloral dans une des veines de l'avant-bras droit. En quelques minutes, le malade tombait dans le même coma que la veille, et la sensibilité disparaissait de nouveau.

» A 11 heures du soir, c'est-à-dire cinq heures et demie après l'injection, je *pus enfoncer une épingle dans la peau des membres et de la poitrine*, sans provoquer le moindre signe de douleur, sans déterminer le moindre mouvement réflexe. Le malade se réveilla à 2 heures du matin : le sommeil anesthésique avait duré huit heures.

» Le lendemain, 11 février, j'ai fait une troisième injection de 9 grammes d'hydrate de chloral, qui a produit absolument la même insensibilité.

» J'ai évité de parler de l'influence que ces diverses injections avaient eu sur l'état tétanique proprement dit, me réservant de publier l'observation de ce fait quand l'issue de la maladie sera connue. Je me contente de dire, pour le moment, que mon malade est arrivé au onzième jour, et que le tétanos paraît notablement amélioré. »

A 5 heures et demie, l'Académie se forme en Comité secret.

La séance est levée à 6 heures un quart. É. D. B.

COMPTES RENDUS

DES SÉANCES

DE L'ACADÉMIE DES SCIENCES.

SÉANCE DU LUNDI 2 MARS 1874.

PRÉSIDENCE DE M. BERTRAND.

PHYSIOLOGIE PATHOLOGIQUE. — *De l'anesthésie produite chez l'homme par les injections de chloral dans les veines* (suite). *Tétanos traumatique traité par les injections. Guérison.* Note de M. ORÉ, présentée par M. Bouillaud. (Extrait.)

« J'ai l'honneur de présenter à l'Académie la suite de l'Observation dont je l'ai déjà entretenue (p. 515 de ce volume). Je reviens d'abord, en quelques mots, sur l'état dans lequel je trouvai le malade avant la troisième injection de chloral, c'est-à-dire au point où s'arrêtait ma précédente Communication.

» Le 11 février, à 9 heures du matin, le malade est dans une sorte de coma. Il paraît abattu et répond mal aux questions qu'on lui adresse. La contracture des mâchoires est plus prononcée que la veille, ainsi que l'opisthotonos; il présente des crises convulsives, assez fréquentes et prolongées. C'est alors que je me décide à faire une troisième injection de 10 grammes de chloral, qui est suivie du même calme, du même sommeil, de la même anesthésie que les précédentes. Je l'ai revu à midi, 3 heures, 7 heures, 9 heures. A minuit, il était notablement mieux; le pouls et la respiration offraient leur rhythme normal. Je me hâte de dire que j'ai profité des rares moments où le sommeil semblait disparaître pour faire prendre des potages au tapioca.

» Le 12 février, la nuit a été très-bonne; le malade est calme; le facies n'est plus abattu; les membres inférieurs sont devenus souples, ainsi

que les parois abdominales. Le malade a uriné abondamment. L'amélioration est si manifeste, pour tous ceux qui ont suivi ma visite, que je ne crois pas devoir renouveler l'injection, et que je me contente de prescrire une potion avec 4 grammes de bromure de potassium.

» Le 13 février, la nuit a été mauvaise; le malade a été tourmenté par des crises fréquentes de suffocation, occasionnées par une contracture violente des parois de la poitrine. Je crus devoir recourir à une quatrième injection; mais, au moment où j'introduisais la canule dans la veine, il fut pris d'une crise de suffocation, accompagnée de cyanose, qui dura près de cinq minutes.

» Je jugeai prudent de m'abstenir, et je prescrivis, pendant les deux jours qui suivirent, 28 grammes de chloral dans 120 grammes de sirop de Tolu, qui furent donnés par l'estomac. Cette dose, très-élevée, amena seulement de la somnolence, sans produire de modification dans l'état des phénomènes tétaniques. La moindre pression exercée sur la surface du corps suffisait, en effet, pour déterminer des mouvements réflexes. Le dégoût, d'une part, et la fatigue que cette substance amena du côté de l'estomac me firent en suspendre l'emploi.

» Du reste, à partir de ce moment, le malade, auquel on avait imprudemment enlevé un gilet de laine, sans le remplacer, fut atteint d'une *bronchite aiguë*, contre laquelle je dus lutter avec d'autant plus d'énergie, que les phénomènes de contracture des parois thoraciques semblaient dominer tous les autres phénomènes tétaniques. Le kermès, combiné à l'acétate d'ammoniaque à haute dose et à la belladone, firent tous les frais du traitement. J'employai aussi l'opium, à la dose de 15 centigrammes par jour pendant trois jours; il amena de la fatigue, et je fus obligé d'y renoncer. Je restai alors, tout en combattant les accidents bronchiques, témoin de phénomènes convulsifs qui semblaient s'atténuer de jour en jour. La contracture n'était plus, en effet, un état permanent; elle revenait au contraire par crises de courte durée, portant tantôt sur les membres inférieurs, tantôt sur les parois abdominales, tantôt sur les muscles des lombes, du cou ou des mâchoires: elle cessait presque aussitôt pour faire place au relâchement; quoi qu'il en soit, j'étais disposé à recourir aux injections, si elles devenaient nécessaires. Il n'en a pas été ainsi, et, aujourd'hui, 28 février, le malade est en pleine convalescence: il s'asseoit dans son lit, peut se coucher indifféremment sur le côté droit et le côté gauche; les membres inférieurs, ainsi que les parois thoraciques et abdominales, ont repris leur souplesse habituelle; le sommeil est bon, l'appétit revenu : le malade a pu

commencer à manger des aliments solides; toutes les fonctions s'accomplissent, du reste, avec une parfaite régularité. Il a même demandé à rentrer dans sa famille, ce que j'ai refusé d'accorder par excès de précaution.

» Trois conséquences découlent de ce fait :

» 1° *L'innocuité des injections intra-veineuses de chloral.* Nous n'avons pas observé chez ce malade la plus légère trace de phlébite; il y a eu un petit abcès, à forme spéciale, qui s'est produit à la partie inférieure de l'avant-bras droit, par suite de la pénétration du chloral dans le tissu cellulaire.

» Mes expériences sur quatre animaux m'ont appris qu'il en est toujours ainsi, quand la dose est élevée. Cela conduit à cette conclusion importante pour le clinicien, que la méthode sous-cutanée constitue la voie la plus défectueuse pour l'administration du chloral. Si la quantité injectée dans le tissu cellulaire est faible, elle sera absorbée sans produire d'accidents locaux, mais aussi sans produire aucun résultat sur l'organisme. Si, au contraire, elle est élevée, elle amène des abcès : dans le premier cas, elle est inutile; dans le second, elle est nuisible.

» 2° Une seconde conséquence se tire de l'insensibilité absolue, si rapide et si longue, que produit cette substance lorsqu'elle est mise *immédiatement en contact avec le sang;* j'en ai déjà parlé, je n'y reviendrai pas.

» 3° L'hydrate de chloral *administré par la voie veineuse* a triomphé rapidement des accidents tétaniques. Trois injections de 10 grammes, répétées pendant trois jours, à vingt-quatre heures de distance, ont déterminé avec le sommeil *la paralysie complète de la sensibilité et de la motilité.* Du reste, ces phénomènes, présentés par le malade, ne sont que la reproduction fidèle de ceux que j'avais observés dans mes nombreuses recherches. Aussi puis-je affirmer que l'expérience clinique a confirmé, de tous points, l'expérience du laboratoire. L'importance de cette affirmation ne saurait passer inaperçue, car elle démontre une fois de plus, avec la possibilité de conclure de l'animal à l'homme, les ressources immenses que la Physiologie expérimentale peut fournir au clinicien et au thérapeutiste.

» Mais ce qui est surtout digne de remarque, et j'insiste particulièrement sur ce point, c'est *la faible quantité de chloral* qu'il a fallu employer pour amener un résultat favorable. On avait objecté à la méthode des injections intra-veineuses « que les tétanos qui guérissent par cette substance durent » en moyenne vingt-cinq jours, qu'il faut, pour maintenir le malade dans la » narcose, revenir au chloral cinq ou six fois par jour, et qu'il ne serait » pas pratique de faire cinq ou six injections chaque jour, pendant vingt-» cinq jours. » On n'a pas pris garde, en faisant cette objection, que, par

le fait seul de la pénétration *directe* dans les vaisseaux, l'action physiologique du chloral est, en quelque sorte, *décuplée*, et que les effets qu'il produit sur l'organisme sont alors plus rapides, plus sûrs et plus durables. Mes expériences sur les animaux l'avaient prouvé : l'observation de ce malade le démontre d'une manière encore plus péremptoire. Il a suffi, en effet, de trois injections de 10 grammes de chloral pour enrayer les accidents tétaniques. Ce qu'il faut pour guérir le tétanos, ce n'est pas de maintenir le malade dans la narcose pendant vingt-cinq jours, mais de *sidérer* le pouvoir réflexe de la moelle, trop exalté par l'état morbide, au point de le ramener promptement à son état physiologique, et d'empêcher, par suite, la contracture musculaire de devenir générale. C'est là ce que fait le chloral, *mais seulement s'il est administré par la voie veineuse*. Il est impossible d'en douter, quand on a été le témoin de mes expériences et du fait qui précède. Le pouvoir réflexe subit, dans cette circonstance, que l'on me permette cette comparaison, un phénomène analogue à celui que l'on désigne en Chirurgie sous le nom de *choc*. Aussi, pendant les jours qui suivirent la dernière injection, ce pouvoir semblait-il, en quelque sorte, se réveiller; mais ce réveil fut toujours de courte durée, car il provoqua des crises de contracture tout à fait passagères.

» Mais, pour que le chloral injecté dans les veines enraye les phénomènes tétaniques, il faut que la dose administrée soit assez élevée pour *paralyser presque immédiatement l'action réflexe de la moelle et amener momentanément la paralysie complète du mouvement et de la sensibilité*. La dose de 10 grammes à chaque injection m'a paru suffisante pour amener ce résultat. »

Anesthesia in Man Produced by the Intravenous Injection of Chloral*

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(Presented by Dr. Jean Bouillaud)

On May 29, 1872, in a note addressed to the Surgical Society of Paris, I stated:

> "Numerous varied and frequently repeated experiments have taught me that chloral *injected into the veins* constitutes *the most powerful of all anesthetic agents;* 2, 3, 4 or 6 gm. of chloral, according to the weight of the animal, sufficing to plunge the animal into such an insensible state that no stimulant, *except electrical current,* is capable of changing it. This insensibility, which resembles that of the cadaver, lasts one, two, three, five hours; and even if the cerebrospinal axis is momentarily disrupted, in both the sensory and the motor aspects, respiration continues calm and regular. To me, it has been experimentally demonstrated today that chloral, administered by the intravenous method, *is a surgical anesthesic agent far superior to chloroform,* first, because the insensible state produced is infinitely more complete and longer than that brought about by chloroform, and second, because it does not produce any of the worrisome asphyxic phenomena so often observed when chloroform is used."

The experiments on which the preceding assertions are based have been carefully reported in the note which I have submitted to the judgment of the Academy. It remained to be ascertained whether experimentation, when extended from animal to man, would lead to the same result. The following facts will leave, I hope, no doubt in this regard.

I received on my service at the Hospital of Saint Andrew of Bordeaux (room 10, bed 14) a man of fifty-two years, who, after *sustaining a mild crushing injury to the end of the left middle finger,* noted the appearance of a contracture of the muscles of mastication, soon followed by confirmed traumatic tetanus.

When this man entered the hospital, trismus was very marked, and the separation of the jaws did not exceed 5 mm.; the markedly contracted nuchal and cervical muscles permitted no movement in this region; the head was thrown back posteriorly. The limbs and even the trunk still possessed some freedom in their physiologic activity when the patient was at rest, but the slightest effort to move, to speak and to swallow abruptly brought about generalized contractions of the muscular system. At the same time, respiratory and circulatory disturbance supervened, manifested by acceleration of the pulse, dyspnea and incomplete cyanosis. Mental faculties were intact.

A mild contusion was noted at the end of the left middle finger, associated with subungual ecchymosis. *The slightest pressure on this point brought about an exaggeration of the tetanic stiffness and intolerable pains.*

In the presence of such a condition, I did not hesitate an instant to make use of an *intravenous injection of chloral.*

On the ninth of February at 5 p.m., I injected twice, three or four minutes apart, into one of the right radial veins, a solution of 9 gm. of chloral hydrate in 10 gm. of water.

Immediately after the second injection, the patient fell into a tranquil sleep; respiration, at first accelerated, became calm and regular. The pulse, which was counted at 90 beats before the injection, fell to 70; the muscular stiffness disappeared almost completely; the jaws separated up to 3 cm. and permitted the passage of the tongue.

Passage of the fingers over the surface of the skin and even moving of the members of the patient no longer evoked muscular reactions. It was possible to pinch the patient with impunity, without provoking in him the slightest sign of sensibility.

The anesthesia was so complete that I was able to explore surgically at will the crushed finger, an action which, before the injection, caused violent pain.

Passing the fingers over the surface of the skin, and even passive movement of the extremities, no longer brought about reflex convulsions. It was possible to pinch the patient without provoking from him the slightest sign of sensitivity. Feeling that this situation was now under control, I sought to remove the cause of the tetanic phenomena, and decided to perform *avulsion* of the nail. Under the nail I introduced the point of a pair of scissors, which I drew back and forth until the nail was divided in two; then I successively removed each half with forceps. When I had done this, I cleaned up the nailbed with a scalpel. During the whole length of the operation, *ordinarily so painful,* the patient did not make the slightest sign of pain or the least movement.

I saw the patient again at 9 p.m. He was sleeping deeply, and the anesthesia was still in effect. I was able to pinch him forcibly on the lower limbs, on the jaws and *to pass the tip of my index finger over the ocular conjunctiva without producing the slightest reflex movement,* all without awakening him. And, as has been demonstrated today, when this latter phenomenon is produced after the inhalation of chloroform, sensibility is absolutely extinguished.

The patient awakened at 4 a.m.; I did not see him until 9 o'clock. Sensibility by that time had returned, although it was still incomplete, especially in the lower limbs.

On February 10, at 5:30 p.m., I made a second injection of 10 gm. of chloral in one of the veins of the right forearm. In a few minutes the patient fell into the same coma as on the previous day, and sensibility again disappeared.

At 11 p.m.—that is to say, five and one-half hours after the injection, *I was able to insert a pin into the skin of the limbs and into the chest* without provoking the slightest sign of pain and without bringing about the slightest reflex movement. The patient awakened at 2 a.m.; anesthesia had lasted

eight hours.

The next day, February 11, I made a third injection of 9 gm. of chloral hydrate, which produced absolutely the same insensibility.

I have avoided speaking of the influence which these diverse injections have had on the tetanic state proper, preferring to delay publication of these facts until the outcome of the patient shall have been known. I am happy to say that, at the time of this report, my patient has reached the eleventh day and that the tetanus appears markedly abated.

At 5:30 the Academy met in closed session.

It adjourned at 6:15. E. D. B.

Pathologic Physiology

Treatment of Traumatic Tetanus by Injections. I have the honor to present to the Academy further remarks on the observation which I have already presented. In a few words, I shall return at first to the state in which I found the patient before the third injection of chloral; that is to say, at the point at which I terminated my preceding communication.

On February 11, at 9 a.m., the patient was in a sort of coma. He appeared to be dejected, and responded poorly to questions addressed to him. Contracture of the jaws was more pronounced than it had been on the day before, and so was the opisthotonos. Convulsive crises occurred, and were rather frequent and prolonged. It was then that I decided to give a third injection of 10 gm. of chloral. I did so, and it was followed by the same calm, the same sleep and the same anesthesia as before. I saw him again at noon, at 3:00, at 7:00 and at 9:00. At midnight he was notably better; the pulse and respiration had returned to their normal rhythm. I hasten to say that I made use of those rare moments when sleep seemed to have disappeared to induce him to take some tapioca soup.

On February 12, the patient had a very good night; he was calm; his expression no longer was dejected, and the lower legs, as well as the abdominal wall, had become relaxed. The patient urinated abundantly. The improvement was so evident to all those who followed my visit that I decided not to renew the injection, but prescribed a potion, 4 gm. of potassium bromide.

On February 13, the patient had a bad night; he was tormented by frequent crises of suffocation, accompanied by violent contractures of the thoracic wall. I thought it would be necessary to have recourse to a fourth injection, but just as I introduced the cannula into the vein, he was seized by an attack of suffocation, accompanied by cyanosis, which lasted nearly five minutes.

I judged it prudent not to inject more chloral. Instead, I prescribed, for use in the next two days, 28 gm. of chloral in 120 gm. of syrup of tolu, which was given by stomach. This quite high dose led only to somnolence, without producing any change in the tetanic phenomena. Indeed, the least pressure over the body of the patient produced reflex movements. Disgust, in part, and fatigue of the patient's stomach which the agent produced, caused me to stop using it.

At the time of this report the patient had *acute bronchitis*, which arose

after someone imprudently removed from him a linen bed jacket without replacing it. I had to summon even more energy in the treatment of this patient, because the manifestations of contracture of the thoracic cage seemed to dominate all other tetanic phenomena. Antimony oxysulfide, combined with ammonium acetate in high doses, and belladonna, were the agents used. I also administered opium at the rate of 15 centigrams a day for three days; this produced fatigue and so I had to discontinue it. There remained, then, the problem of preventing bronchial accidents indicative of convulsive phenomena, which seemed to attenuate from day to day. Indeed, contracture no longer was present continuously; rather, it returned in crises of short duration, involving sometimes the lower limbs, sometimes the abdominal wall, sometimes the lumbar muscles and sometimes the neck or the jaws. These contractures were followed almost immediately by relaxation; but I was prepared to use the injections, had they become necessary. They did not become necessary, and today, February 28, the patient is well on the road to recovery. He sits up in bed, may lie however he pleases, on the right or left side; the lower limbs as well as the abdominal and thoracic walls have returned to their normal relaxed state. The patient sleeps well and the appetite has returned; he can now take solids; all body functions have returned with perfect regularity. He has even asked to be allowed to return to his family, but I have refused this request because of precaution, which may be excessive.

Three things of consequence are to be noted.

1. *The innocuousness of the intravenous injection of chloral.* We have not observed in this patient more than a slight trace of phlebitis. A small abscess of specific nature was produced on the lower part of the forearm as a result of penetration of chloral into the tissues.

My experiments with four animals proved that it is always thus when the dose of the agent is high. It is important for the clinician to know that the subcutaneous route is the worst that could be used for the administration of chloral. If the subcutaneous dose is weak, the agent will be absorbed without producing local accidents, but also without producing any general effects on the organism. If, on the other hand, the dose is high, it will lead to the formation of abscess. In the former instance the agent is useless; in the latter it is injurious.

2. A second item of consequence may be drawn from the fact of the absolute insensibility, so rapid and so prolonged, which this substance produces when it is placed *immediately in contact with the blood.* I have already spoken of this, and I shall therefore not discuss it further.

3. Chloral hydrate *administered by the intravenous route* rapidly overcomes tetanic accidents. Three injections of 10 gm. each, repeated over three days, twenty-four hours apart, have brought about, with sleep, *complete paralysis of sensitivity and motility.* Moreover, these phenomena as observed in the patient are but the faithful reproductions of those which I have observed in my numerous experiments. Then, too, I can affirm that the results of clinical experiments have confirmed those of laboratory experimentation on all points. The importance of this confirmation of laboratory work should not pass unnoticed, for it affords another excellent example of the possibility of comparing physiologic reactions in the animal with

those in man, by means of which the enormous resources of experimental physiology may contribute to the knowledge of the clinician and the therapist.

But there is one point which I consider worthy of note above all others, and I particularly emphasize this point: it is the *small quantity of chloral* which is necessary to bring about a successful result. Objections have been made that intravenous injections "which are used in the treatment of tetanic patients require on the average twenty-five days, and that it is necessary, in order to maintain the patient in a state of narcosis, to resort to the use of chloral five or six times a day, and that it would not be practical to make five or six injections daily for twenty-five days."

Very likely those who made such objections were not careful, in carrying out injections, to note that *direct* penetration into the vessels increases the physiologic action of chloral by tenfold, and that the effects produced thereby are more rapid, more certain and more lasting. Results of my animal experiments have proved this, and the observations made of this patient have demonstrated it even more convincingly. Indeed, three injections of 10 gm. of chloral have been sufficient to prevent tetanic accidents. Keeping the patient narcotized for twenty-five days is not what is required to cure tetanus. Rather, what is essential is *diminution* of the reflex power of the cord, which has become highly irritable as a result of the disease process. This diminution must proceed to the point of normalcy, to prevent muscular contractures from becoming generalized. It is in this respect that chloral is useful, *but it is useful only if administered by the intravenous route.* On the basis of my experiments and case I have described, there is no longer any room for doubt. The reflex power undergoes a change, if I may be permitted the comparison, similar to the analogous phenomenon observed in what is called *surgical shock.* However, during the days which follow the last injection, there seemed somehow to be a resurgence of this power, but this was always of short duration, for it brought about altogether transitory contractures.

But, for the intravenous injection of chloral to prevent tetanic phenomena, the dose must be sufficiently high *to paralyze almost immediately the reflex action of the cord and summarily to bring about the complete paralysis of movement and sensitivity.* A dose of 10 gm. per injection seems to me to be sufficiently high to accomplish this result.

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Induction of Anesthesia in Man by Intravenous Injection of Sodium Iso-Amyl-Ethyl Barbiturate.

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During the last 6 years the sodium salt of iso-amyl-ethyl barbituric acid has been used extensively as a general anesthetic in animal experiments.[1] The difficulty experienced in preparing strictly uniform solutions of this substance and the tendency of such solutions to deteriorate on standing have heretofore prevented the utilization of this preparation for the induction of general anesthesia in man.

Sodium iso-amyl-ethyl barbiturate may, however, be prepared in a pure, anhydrous form, and if sealed in a glass vessel for protection against moisture and carbon dioxide is perfectly stable even when subjected to severe durability tests. The variations in anesthetic value previously noted appear to have been due in part to impurities, in part to slight variations in the pH value and in part to hydrolysis and decarboxylation on standing in solution.

Highly purified preparations of the sodium salt adjusted so that their 10% solutions in pure distilled water show pH values between 9.5 and 9.8 by the electrometric method, using the Bailey hydrogen electrode, give a maximum anesthetic effect with a minimum degree of toxicity when injected slowly by the intravenous route in dogs. A lowering of the alkalinity to the point at which a 10% solution shows pH values of 9.2 to 9.3, accompanied by the development of a slight opalescence or cloudiness due to commencing separation of

[1] Swanson, Edward E., and Page, Irvine H., *J. Pharm. and Exp. Ther.*, 1927, xxxi, 1.

traces of the barbituric acid compound, causes a striking loss in anesthetic value and a marked increase in toxicity. Such solutions even when slowly injected may cause Cheyne-Stokes breathing and other toxic effects on the respiratory center.

Since the sodium salt of iso-amyl-ethyl barbituric acid is almost entirely converted into the relatively water insoluble barbituric acid at a point considerably above that at which the water phase of the blood is supposedly buffered, pH 7.3 to 7.4, it might be anticipated that the injection of the 10% solution of the salt into the blood stream might easily result in sufficient precipitation to cause respiratory and other disturbances similar to those resulting from the injection of the already opalescent or slightly precipitated solution. There is, however, no trace of any such effect provided the solution is perfect and a given rate of injection is not exceeded, but even a perfectly prepared solution, if injected too rapidly, will affect the respiratory center. These results make it appear highly probable that the affinity of the cell surfaces and other lipoidal components of the blood for the released barbituric acid molecules is such that provided a given rate of injection is not exceeded, the accumulation of the product in the water phase of the blood does not reach the point of incipient precipitation with the accompanying toxic effect on the respiratory center.

40 to 50 mgm. per kilo of this preparation injected slowly by the intravenous route in a dog causes unconsciousness in 3 or 4 minutes and sufficiently deep anesthesia for surgical operation in 20 minutes. This anesthesia lasts for a period ranging from 1 to 3 hours depending on the dose employed. Dogs, when subjected to abdominal and other operations, have not exhibited any evidence of inadequate anesthesia, and the blood pressure has remained unchanged except in those cases in which severe hemorrhage has occurred.

Following anesthesia there is a somewhat prolonged period of post-operative sleep from which the dog may usually be aroused. However, it appeared desirable, before using this preparation extensively for the induction of general anesthesia in man, to find some means of antidoting or counteracting the post-anesthetic effects This has been accomplished in dogs by injecting intramuscularly 1 mgm. ephedrine sulphate per kilo followed by 5 mgm. caffeine sodium benzoate per kilo. Dogs which have received such injections shortly after operation, when subsequently presented with food, will sniff the food, begin to eat and exhibit other signs of consciousness, whilst control dogs which have not received such injections may fail to react to the food.

This purified preparation of Sodium iso-amyl-ethyl barbiturate

has given excellent results in the induction of general anesthesia in man in about 300 cases. The surgical anesthetic dose for man appears to be considerably smaller than that for the dog and ranges from 20 to 25 mgm. per kilo. There is no definite information available regarding the lethal dose of this preparation for man, but such meagre information as may be gathered from attempts at suicide, etc., makes it appear probable that the ratio between lethal and anesthetic dose is higher for man than for the dog. However, in the absence of any definite information regarding this point extreme caution has been observed in the conduct of these experiments and the dose employed has seldom exceeded 1.25 to 1.5 gm.

A dose of 10 to 15 mgm. per kilo has generally produced adequate anesthesia for satisfactory and unembarassed manipulations in minor surgery. This dose has also sufficed for the control of convulsions in eclampsia, strychnine poisoning, epilepsy, tetanus and rabies, for periods of 6 to 10 hours.

20 to 25 mgm. per kilo have been employed to produce complete surgical anesthesia in cases in which other general or local anesthetics were contraindicated or inconvenient to administer, *e. g.*, mastoidectomy and operations on the face. However, for surgical anesthesia, wherever possible, this preparation has been used in conjunction with other general or local anesthetics.

The intravenous injection of from 12 to 20 mgm. of this preparation per kilo prior to the administration of ether or nitrous oxide and oxygen, has generally made it possible to reduce the amount of the supplementary anesthetic required to 20% or 25% of the quantity usually employed.

A similar dose used in conjunction with procain infiltration of the skin has permitted of extensive surgery of the abdomen with a greater degree of anesthesia and more muscular relaxation than when procain was used alone. It has seldom been found necessary in such cases to infiltrate the muscles and deep tissues with procain. The use of this combination seemed particularly advisable in those patients which were poor anesthetic risks.

The action exerted by Sodium iso-amyl-ethyl barbiturate when injected intravenously in diminishing the toxic and convulsive effects of local anesthetics, particularly procain, as recently reported by Loevenhart, Knoefel and Herwick,[2] and by Isenberger,[3] affords a further argument for the use of this preparation in combination with local anesthetics.

[2] Knoefel, P. K., Herwick, R. P., and Loevenhart, A. S., *J. Pharm. and Exp. Therap.*, 1928, xxxiii, 265.

[3] Isenberger, Robert M., *Proc. of the Staff Meetings of the Mayo Clinic*, 1928, iii, 40, 294.

In surgery of the thyroid gland the technique of inducing anesthesia in the patient's room and without his knowledge, thus eliminating psychic stimulation of operating room and personnel, appeared highly desirable.

It is of the utmost importance that the preparation should be in perfect solution before being injected and that the rate of administration intravenously should not greatly exceed 1 cc. per minute. The patient is usually carried rapidly through the stages of anesthesia, so that excitement and laryngeal spasm are rarely observed. Sleep, as a rule, commences within 3 to 5 minutes and surgical anesthesia with complete relaxation of the muscles, and loss of the common reflexes except the pharyngeal, sphincters, etc., occurs within 15 to 20 minutes after starting the injection. The respirations are those of a patient in profound sleep, more often increased than decreased in rate, somewhat diminished in amplitude but regular. The blood pressure may decrease 15 to 30 mm. during the time of injection but rapidly regains its previous level.

Surgical anesthesia lasts for a period of 1 to 3 hours dependent in some measure on the dose employed. After maximal anesthetic doses the patients may sleep from 3 to 10 hours and occasionally longer. Nausea, retching and vomiting have not been observed in any of the cases. Frequently patients when coming out of sleep become restless before they are fully conscious. Morphine administered in the usual amounts exerts a quieting effect.

In those cases in which maximal anesthetic doses have been employed, in which it is desired that the patient should awake somewhat sooner and fully alert mentally, 25 to 50 mgm. of ephedrine sulphate injected intramuscularly, followed by 0.65 to 1 gm. sodium caffeine benzoate, one-half to 2 hours after the operation, has exerted the desired effect.

Detailed papers covering the clinical, pharmacological and biophysical-chemical aspects of the case will shortly be published.

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tionen erleiden; sie mögen ihren Defekt vernachlässigen. Zeigen sich aber die erwähnten Komplikationen, und mögen es nur leichte Beschwerden sein, oder begeben sie sich gerade beim Reisen in eine erhöhte Gefahrzone, so sollte Salzsäure in irgendeiner Form regelmäßig genommen werden, möglichst wenig unter der Vorstellung einer bestimmten Medikation, sondern als „Limonade" ohne Limonen — Zitronen —, ja ich gehe noch weiter und meine, daß auch der Magengesunde namentlich in der Fremde sich besser als an ein alkalisches Tafelwasser an eine Salzsäurelösung halten sollte. Er kann ein zweifelhaftes Trinkwasser ziemlich zuverlässig sterilisieren, wenn er die Salzsäure etwa eine Stunde vor dem Trinken zu seinem Trinkwasser fügt oder sich eines zuverlässig sterilen Tafelwassers bedient, das nicht alkalischer ist als das gewöhnliche Leitungswasser, sie sind freilich selten, dem er die Salzsäure zufügt. Erlebt man so oft, wie von Auslandsreisen, besonders nach dem Süden, Menschen mit Magen-Darmstörungen zurückkommen, so ist es wohl berechtigt, auf diese Prophylaxe auch für den Gesunden hinzuweisen. Wichtiger für die Klinik bleibt uns selbstverständlich, daß der kranke Achyliker, also ganz besonders jene Achylikergruppe, die Beschwerden hat oder gar objektive Krankheitssymptome, über den Salzsäuremangel hinaus, bietet, so mit einer Substitutionstherapie behandelt wird, daß die Dosen ausreichend bakterizid wirken und die peptische Vorverdauung im Magen vollziehen. Liegen Indikationen vor, den Harn sauer zu machen, so haben wir wohl bessere Möglichkeiten als die der HCl-Therapie, dennoch ist auch diese Wirkung bei jeder Salzsäuretherapie zu beachten.

Mag das alles nichts Neues sein; daß es bisher so oft nicht genügende Berücksichtigung findet, darüber ist nach meiner Erfahrung in Klinik und Praxis kein Zweifel, und deshalb besteht die Berechtigung, gerade auch beim Auftauchen eines neuen Präparates, das sich mir bewährt hat, wieder auf die Wichtigkeit jener *Substitutionstherapie*, die weit über die Organbehandlung hinausgeht, nachdrücklich hinzuweisen.

v. Bergmann, Funktionelle Pathologie. Springer, 1932; dgl. Handbuch der Inneren Medizin, Band III. — Gutzeit, M. m. W. 1932 Nr. 26. — Kalk, Das Geschwür des Magens und Zwölffingerdarms. Urban & Schwarzenberg, 1931. — Katsch, Handbuch der Inneren Medizin, Band III, 2. Aufl. — Kauffmann, Neue deutsche Klinik, 1930, Bd. VII, Lief. 31; dgl. D. m. W. 1932 Nr. 7. — Tagawa, Biochem. Z. 1930, 243 S. 330. — Wantoch, M. m. W. 1931 Nr. 22.

Pharmakologie des intravenösen Kurznarkotikums Evipan-Natrium

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In meiner pharmakologischen Einführungsarbeit über die von Dr. Kropp und Dr. Taub in den Elberfelder chemischen Laboratorien aufgefundene C-C-Cyclohexenylmethyl-N-methyl-barbitursäure, das Einschlafmittel „Evipan" [1], habe ich bereits darauf hingewiesen, daß diese Barbitursäure im Tierexperiment ungewöhnlich rasch und ohne Erregungserscheinungen einen kurzen, aber tiefen Schlaf ohne Nachwirkungen hervorruft. Nach größeren Dosen vertieft sich die Schlafwirkung zur Narkose. Erst ein Vielfaches der narkotischen Dosis ist tödlich. Diese Beobachtungen führten zu der Überlegung, daß sich das „Evipan" als *injizierbares Narkotikum für Kurznarkosen* eignen müsse, wenn es gelingt, daraus injizierbare Lösungen herzustellen. Diese Anforderung erfüllte das Natriumsalz des „Evipan", welches eine farblose, spielend in Wasser lösliche Substanz ist. Zudem fanden wir intravenös injizierbare organische Lösungsmittel, in denen es dauernd haltbar ist.

Eine eingehende tierexperimentelle Untersuchung des Evipan-Natrium (E.-Na) auf seine Eignung als injizierbares Kurznarkotikum schien um so gerechtfertigter, als unter den gegen die Inhalationsnarkotika andrängenden nichtflüchtigen Narkotika noch kein Mittel für Kurznarkosen gefunden wurde. Eine *Verdrängung des Ätherrausches* durch eine die Psyche des Patienten schonende Injektionsnarkose von etwa 5—15 Minuten Dauer unter Verzicht auf völlige Entspannung der Bauchdecken dürfte Ärzten und Patienten gleich willkommen sein. Die nachfolgende pharmakologische Analyse zeigt, daß das E.-Na in der Lage ist, gegen den Ätherrausch anzugehen.

Von den gebräuchlichen Laboratoriumstieren stehen *Katzen* in ihrem Verhalten gegen Narkotika dem Menschen am nächsten. Injiziert man einer Katze eine narkotische Dosis von E.-Na in 10%iger Lösung im Verlauf von 2 Minuten in eine Vene, so wird das Tier schon nach der ersten Minute ohne dazwischentretende Exzitationserscheinungen müde und schlapp, der Kopf sinkt herab, die Atmung wird langsamer und tiefer, bleibt aber regelmäßig. Mit dem Abschluß der Injektion hat sich der der Dosis entsprechende maximale narkotische Zustand bereits voll entwickelt. Die Schleimhäute (Zunge) bleiben bis zur tödlichen Grenzdosis (D. l. m.) rosig. Ist die D. l. m. erreicht oder überschritten, so tritt der Tod immer an Atemstillstand ein. Nach eben narkotischen Dosen erwachen die Tiere auffallend rasch. Erst wenn die vollnarkotische Dosis (Stadium VI, s. Tabelle) überschritten wird, verzögert sich das Erwachen. Während des Erwachens der Katzen wird auch bei der E.-Na-Narkose (E.-Na-Na.) das für Barbitursäuren charakteristische feinschlägige Zittern und fibrilläre Zucken beobachtet. Einzelheiten über die Intensität und die Abebbung der Narkose an Katzen sind aus der folgenden Tabelle zu ersehen.

Dosis E.-Na mg/kg	Maximale Narkosetiefe	Abebbung der Narkose nach Minuten: Eintritt in Stadium III (Erwachen)	Eintritt in Stadium I (Ataxie)	Spontanes Laufen	Geringste Atemfrequenz, Prozent der Ausgangswerte
20	III	—	23	30	75
20 [2]	V—VI	11	29	35	70
25	V—VI	8	33	64	77
30	VI	49	121	180	45
60	VI	65	350	370	49
90	VI	190			40 selten vorübergehende künstliche Atmung
100—110	D. l. m.				

Die Narkosestadien sind nach dem jeweiligen Zustand der Stell- und Bewegungsreflexe (Magnus) entsprechend dem Schema von Girndt bezeichnet. Im Stadium I laufen die Tiere schwankend bei normaler Sitzhaltung. Das Stadium III, Seitenlage bei erhobenem Kopf, entspricht ungefähr dem Erwachen des Menschen aus der Narkose. Stadium V mit dem eben erlöschenden Kornealreflex und den stark abgeschwächten Rückenmarksreflexen entspricht einigermaßen der Rauschnarkose. Stadium VI mit seiner völligen Reflexlosigkeit stellt tiefe Vollnarkose dar. Die Zeitangaben sind Mittelwerte aus mindestens 3 Versuchen.

Wesentlich und für ein intravenöses Narkotikum neu ist die *Geschwindigkeit* und die *Kürze der Wirkung.*

Das Erwachen (Stadium III) erfolgt selbst nach Dosen, die der Rauschnarkose (Stadium V) entsprechen, im Verlauf von rund 10 Minuten. Nach insgesamt 30—60 Minuten laufen die Tiere unbeeinträchtigt spontan umher. Erst nach Dosen, die über der vollnarkotischen Grenzdosis liegen, verlängert sich die Abebbung. Am Kaninchen sind die Abebbungszeiten kürzer, am Hunde etwas länger.

Als zweites Charakteristikum des E.-Na ist seine *große therapeutische Breite* hervorzuheben.

Mit 25 mg/kg Tier wird an der Katze, mit 30 mg am Hund stets Rausch-, häufig aber Vollnarkose erzielt. Die D. l. m. liegt jedoch bei 100—110 mg E.-Na pro Kilogramm Katze. Somit beträgt die therapeutische Breite an der Katze 4, am Hund 3,3. Beschleunigte Injektion des Narkotikums steigert infolge stärkerer Überflutung des Zentralnervensystems mit Narkotikum die Wirkungsintensität und Geschwindigkeit.

Das E.-Na gehört als nichtflüchtiges Narkotikum zu den unsteuerbaren Narkotika, denn sein Wirkungsabfall ist nicht Folge seiner Abatmung, sondern seines chemischen Abbaues im Organismus. Zeitlich betrachtet, spielt sich dieser Entgiftungsprozeß aber so rasch ab, daß im Effekt (nicht im Wirkungsmechanismus) das E.-Na eine erhebliche Annäherung an die steuerbare Äthernarkose bedeutet. Hinsichtlich der Anflutungsgeschwindigkeit ist es dem Äther überlegen und in dieser Hinsicht den gasförmigen Narkotika nahezustellen.

Die Geschwindigkeit des *E.-Na*-Abbaues beleuchtet folgender Kaninchenversuch: Durch die Injektion 40 mg/kg Tier wird Stadium V erreicht. Abebbung nach 13 Minuten auf Stadium III. 20 mg/kg nachgespritzt: Stadium V. Nach 13 Minuten auf Stadium III abgeflacht usw. Von einem Tier von 2,4 kg Gewicht werden also in rund 13 Minuten 46 mg E.-Na unwirksam gemacht. Bei höheren Anfangsdosen geht dieser Prozeß entsprechend der Vertiefung der Narkose langsamer vonstatten

Eine wesentliche Rolle bei dem Abbau des E.-Na spielt die *Leber*, da hepatektomierte (eviszerierte) und lebergeschädigte (phosphorvergiftete) Tiere außerordentlich viel langsamer erwachen. Die Niere ist an diesem Prozeß weder als Organ des chemischen Abbaues (uranvergiftete und nephrektomierte Tiere) noch als Ausscheidungsorgan beteiligt, da im Harn nur Spuren unveränderten E.-Na nachweisbar sind. Auch im Blut wird E.-Na kaum zerstört. Daß E.-Na und seine Abbauprodukte auch bei wiederholtem Gebrauch unschädlich sind, erwiesen Gewöhnungsversuche, in welchen Tieren während mehrerer Monate täglich hypnotische Dosen E.-Na injiziert wurden.

Unter den *akuten Nebenwirkungen* eines Narkotikums spielen neben der bereits geschilderten Dämpfung der Atmung (siehe Tabelle) die Kreislaufveränderungen die Hauptrolle: Am nicht narkotisierten Kaninchen sank d Blutdruck für wenige Minuten um höchstens 15 bis 20 mm Hg, ähnlich am urethanisierten Tier. Die Schöpfarbeit isolierten Hundeherzens nahm nach 50 mg E.-Na um nur 3% Es ist daher begreiflich, daß nach kurzem Atemstillstand inf Überdosierung das Herz der Tiere kräftig und regelmäßig wei schlägt. Minimal ist die Stoffwechselhemmung und die Senkung Körpertemperatur während der E.-Na-Na. Auch die Alkalires wird kaum verändert; der Blutzuckerspiegel bleibt normal. Er chen wurde nie beobachtet.

Lokal wird E.-Na reizlos vertragen (Kaninchenquaddel), auch injizierte Vene bleibt unverändert und durchgängig. Hämolyse kor praktisch nicht in Frage.

Morphinvorbehandlung vertieft und verlängert meist auch die V kung subnarkotischer E.-Na-Dosen, sie setzt jedoch die Vert lichkeit vollnarkotischer Dosen herab.

Durch Kohlensäureinhalation kann die durch verträgliche E.- Dosen verringerte Atemfunktion jederzeit stark gefördert werden Das E.-Na wird in haltbarer, gelöster, vor der Injektion zu dünnender Form abgegeben. Als Lösungsmittel dient der Met diglykoläther, dessen geringe Eigenwirkungen die E.-Na-Na keiner Weise beeinflussen.

Auf Grund dieser tierexperimentellen Unterlagen hielten uns für berechtigt, das E.-Na als intravenöses Kurznar tikum der klinischen Prüfung zuzuführen. Im Verlaufe ei Jahres wurden nach vielversprechenden Anfangsversuch *rund 10 000 E.-Na-Narkosen ausgeführt. In den Berich über diese 10 000 Narkosen befindet sich kein einziger Fall, dem lebensbedrohende Zustände oder gar der Tod infolge E.-Na-Narkose eingetreten wäre.*

Ungeklärt blieb lediglich die Ursache eines plötzlichen Exitus n Abrasio eines septischen Abortes, die in einer mit nur 5 ccm, d. h. halben üblichen Dosis ausgeführten E.-Na-Na. gemacht wurde.

Zusammenfassung. In Tierversuchen wurde nach wiesen, daß das Evipan-Natrium ein intravenös injizierba echtes Narkotikum für Kurznarkosen darstellt, dessen Wirku steil anflutet und ebenso abebbt. Die therapeutische Breite ausnehmend groß. Das E.-Na wird nicht ausgeschieden, s dern im Organismus (Leber) chemisch abgebaut. Es ist lo reizlos verträglich. Die pharmakologische Analyse rechtferti die Übergabe des Präparates an die Kliniker.

Aus der chirurg. Abteilung des Martin-Luther-Krankenhauses in Berlin-Grunewald

Über eine neue intravenöse Narkose mit Evipan-Natrium

Von Prof. WILHELM BAETZNER

Mitte März 1932 wurde mir ein von Weese im Elberfelder Pharmakologischen Institut der I. G. Farbenindustrie Akt.-Ges. ausgearbeitetes *intravenöses Narkosemittel* für Rausch- und Basisnarkosen übergeben. Nach den tierexperimentellen Vorarbeiten sollte der Vorzug des Mittels seine kurze aber intensive Wirksamkeit bei großer therapeutischer Breite sein.

Meine ersten Vorversuche am Menschen fielen vielversprechend aus. Sie veranlaßten mich, bis jetzt 400 Narkosen bei den verschiedensten landläufigen chirurgischen Eingriffen auszuführen.

Dabei waren etwa 220 Laparotomien (Cholezystektomien, Appendizitiden, Magenoperationen, Darmtumoren, Nierenerkrankungen, Prostatektomien), 45 Hernien, 30 Gelenk- und Knochenoperationen, 10 Mammaamputationen, 4 Strumen, 1 Kehlkopfexstirpation, 1 retropharyngealer Halstumor, 40 eitrige Prozesse und eine Reihe verschiedener kleiner Eingriffe, besonders Frakturstellungen.

Ich bin an die Versuche mit der festen Absicht herangegangen, nichts zu riskieren und jede Störung unter allen Umständen habe Höchstgrenzen vermieden. So bin ich jetzt auch in Lage, den Mitteilungen über die neue Narkose voranzustell daß wir *bei allen 400 Narkosen nicht eine einzige ernste S rung* oder gar einen lebensbedrohenden Zwischenfall geh haben. Anderseits ist es ja verständlich, daß eine Reihe Narkosen, weil mit zu kleinen Dosen ausgeführt, nicht ge gend tief und auch zeitlich nicht ausreichend waren und deshalb frühzeitig *Zusatznarkosen* mit Äther bzw. Äthylchlo nötig wurden. Mit wachsender Erfahrung konnten wir sicherer vorgehen, haben gelernt, die vorhandenen narkotisch Wirkungen des Mittels besser auszunützen und sind heute stande, bestimmte *Richtlinien* für die neue Narkose anzugeb Es ist außerordentlich wichtig, die Injektion in die Vene s *langsam* auszuführen, so, daß die Injektion 60—90 Sekun dauert. Während der Injektion unterhält man sich mit d Kranken, der bereits auf dem Operationstisch lagert. M schon nach der Injektion der ersten Kubikzentimeter hört Kranke mitten im Worte zu sprechen auf, die Augen fal

Pharmacology of Short-acting Intravenous Anesthetic Agent, Evipan Natrium

(Evipal Sodium)

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In my pharmacologic introduction on the subject of the sleep-inducing agent "evipan"† (C-C-cyclohexenylmethyl-N-methyl barbituric acid, synthesized by Drs. Kropp and Taub of the Chemical Laboratories in Elberfeld), I pointed out that this barbituric acid induces in animals a short but deep sleep, unusually rapidly, without any signs of excitation and without any aftereffects. Larger doses deepen this sleep to anesthesia. Only a multiple of the anesthetic dose is fatal.

These observations led to the idea that evipan should be suitable as *an injectable, short-acting anesthetic agent* if it were possible to produce it as an injectable solution. These requirements were fulfilled by the sodium salt of evipan, which is a colorless substance easily soluble in water. We also found intravenously injectable solvents in which the agent remains permanently stable. A detailed experimental study of evipan sodium in regard to its suitability as an injectable short-acting anesthetic agent seemed the more justified since amongst the nonvolatile narcotics no agent suitable for short anesthesia was found which could compete with the inhalation anesthetics. It should be equally welcome to physicians and patients to have a *short-acting ether analgesic agent replaced* by anesthesia of five to fifteen minutes' duration, produced by injection, which is less of an affront to the psyche of the patient, without complete relaxation of the abdominal wall. The following pharmacologic analysis shows that evipan sodium is in a position to compete with ether analgesia.‡

Among the commonly used laboratory animals, the cat is closest to man in regard to its reaction to narcotic agents. When a narcotic dose of a 10 per cent solution of evipan sodium is injected intravenously into a cat over a period of two minutes, the animal becomes tired and weak after the first minute, but without any signs of excitation. The head drops and respiration becomes slower and deeper, but remains regular. When the injection is completed, the maximal state of anesthesia in relation to this dose has fully developed. The mucous membranes (tongue) remain pink until the minimal lethal dose has been reached. When the minimal lethal dose has been reached or exceeded, death is always due to respiratory arrest. Yet the animals recover with notable rapidity from narcotic doses. Only if the full anesthetic dose (stage VI, see table) is exceeded, is the recovery of consciousness delayed. The fine tremor and the muscle fibrillations characteristically produced by barbituric acids also were observed during the recovery of the cats from anesthesia with evipan sodium. Details in regard to the intensity of anesthesia and the recovery in cats are summarized in the following table.

TABLE

Dose of Evipan Sodium mg. per kg. Body Weight	Anesthesia, Maximal Depth Stage	Recovery from Anesthesia, Minutes After Injection: Return to Stage III (Awakening)	Return to Stage I (Ataxia)	Walking Spontaneously	Lowest Respiratory Rate in Per Cent of Original Values
20	III		23	30	75
20*	V-VI	11	29	35	70
25	V-VI	8	33	64	77
30	VI	49	121	180	45
60	VI	65	350	370	49
90	VI	190			40
100-110	Minimal lethal dose				Rarely temporary artificial respiration

* In this case the duration of injection was one minute; in all other cases it was two minutes.

The stages of anesthesia are designated according to the prevailing state of the postural and motor reflexes (Magnus), on the basis of the classification of Girndt. During stage I the animals walk unsteadily, but have a normal sitting position. In stage III the animal has a lateral position, with elevated head; this corresponds approximately to the awakening of human beings from anesthesia. In stage V the corneal reflexes are almost abolished, and spinal reflexes are greatly diminished, resembling closely the effects of light surgical anesthesia. In stage VI the complete loss of reflexes represents complete surgical anesthesia. The time values given in the table represent the mean of at least three experiments.

Important, and new qualities in the case of an intravenous anesthetic agent, are the *speed of action* and *short duration* of the drug.

Return to consciousness (stage III) follows in the course of about ten minutes, even after doses which produce light anesthesia (stage V). After a total of thirty to sixty minutes the animals run about spontaneously and unimpaired. Return to consciousness is prolonged only after doses which exceed the dose required for complete anesthesia. In the rabbit the return to consciousness is shorter; in the dog it is somewhat longer.

In addition, special attention should be called to the *wide therapeutic range* of evipan sodium. When a dose of 25 mg. per kilogram of body weight is given to the cat and a dose of 30 mg. per kilogram is given to the dog, light anesthesia is always produced and complete anesthesia frequently is brought about. But the minimal lethal dose is 100 to 110 mg. of evipan sodium per kilogram of body weight for the cat. Thus, the therapeutic range is 4 for the cat and 3.3 for the dog. Rapid injection of the agent increases the intensity and speed of action as a result of the increased flooding of the central nervous system with the anesthetic agent.

As a nonvolatile narcotic agent, evipan sodium belongs to the noncontrollable anesthetics, since the loss of its effect is not a result of elimination by respiration, but rather, of chemical breakdown. Yet this process of detoxification is so rapid that, if the time is considered, the effect (not the mechanism of action) of evipan sodium represents a considerable approximation of the effect of controllable ether anesthesia. In respect to the speed of the onset of action, evipan sodium is superior to ether, and it ranges close to the gaseous anesthetic agents in this quality.

The following experiment with rabbits illustrates the rapid breakdown of evipan sodium. Stage V is reached with the injection of 40 mg. of the agent per kilogram of body weight; recovery as denoted by stage III is reached after thirteen minutes. Again, 20 mg. per kilogram of body weight is injected, resulting in stage V anesthesia. After thirteen minutes anesthesia has lightened to stage III, and so forth. Hence, the system of an animal weighing 2.4 kg. renders 46 mg. of evipan sodium ineffective within about thirteen minutes. When higher initial doses are employed this process is slower, corresponding to the depth of anesthesia attained.

The liver plays an important part in the breakdown of evipan sodium, since hepatectomized (eviscerated) animals and animals with damage to the liver (phosphorus poisoning) regain consciousness considerably slower than do those without such injuries. The kidney takes no part in this breakdown process of evipan sodium, either as a mechanism of chemical breakdown (uranium-poisoned and nephrectomized animals) or as an organ of excretion, since only traces of unchanged evipan sodium are detectable in the urine. There is very little destruction of evipan sodium in the blood. Experiments in tolerance of the agent, in which hypnotic doses of evipan sodium were injected daily over a period of several months, proved that this agent and its breakdown products are not harmful.

In the acute side effects of an anesthetic agent circulatory alteration plays an important part, in addition to the effect of depression of the respiration, already mentioned (see Table). In the nonanesthetized rabbit the blood pressure decreased by 15 or 20 mm. of mercury, at the most, for a few minutes, similar to what takes place in animals under the influence of urethane. The pumping action of the isolated dog's heart was decreased by only 3 per cent after the use of 50 mg. of evipan sodium. It is therefore understandable that, after a brief respiratory arrest caused by overdosage, the heart of the animal which has received evipan sodium continues to beat strongly and regularly. Metabolic depression is minimal, and so also is the lowering of body temperature during anesthesia with evipan anesthesia. The alkaline reserve is scarcely altered; the values for blood sugar remain normal. Vomiting was never seen.

Injected locally, evipan sodium is tolerated without irritation (a skin wheal was raised in rabbits). The vein into which the agent is injected remains unaltered and patent. Hemolysis is practically out of the question.

The effect of pretreatment with morphine is chiefly to deepen and to prolong the effect of subnarcotic doses of evipan sodium; however, this does reduce the tolerance to fully anesthetic doses.

The depression of respiratory function, if it occurs when tolerable doses of evipan sodium are used, can be ameliorated by the inhalation of carbon dioxide. Evipan sodium is produced as a stable solution which is to be diluted before use. Methyl diglycol ether [diethylene glycol monomethyl ether] serves as a solvent; it has little effect of its own, and does not influence anesthesia with evipan sodium in any way.

On the basis of this experimental evidence we felt justified in carrying out a clinical trial of evipan sodium as a short-acting agent for intravenous anesthesia. After promising initial trials, *about 10,000 sessions of anesthesia with evipan sodium were produced in the course of a year. The reports of these 10,000 sessions of anesthesia contain not a single case in which a condition* endangering life, or in which death, was due to anesthesia with evipan sodium.

In only one case does the cause of sudden death, which followed curettage for septic abortion, remain unexplained. For this procedure only 5 cc. of evipan sodium was used for the anesthesia. That is one half the usual dose.

Summary

It has been shown in animal experiments that evipan sodium is a true, short-acting anesthetic agent for intravenous administration. The onset of action is rapid, and recovery from it is similarly rapid. Its therapeutic range is exceptionally wide. Evipan sodium is not excreted as such, but is chemically broken down in the organism (liver). Locally, it is not irritating. The results of pharmacologic analysis justify the placing of this agent in the hands of clinicians generally.

English translation reprinted from Faulconer A, Keys TE: FOUNDATIONS OF ANESTHESIOLOGY, Volume II: 979-982.

PROCEEDINGS

OF THE

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CONTENTS

PLASTIC OPERATIONS ON THE GENITO-URINARY TRACT I. OPERATIONS ON THE URETERS AND KIDNEYS*

Waltman Walters, M. D., Division of Surgery: Before beginning the discussion I would like to present a case in which anomaly was associated with carcinoma and therapeutically induced fistula.

Case 1.—The patient, aged forty-two years, was a Peruvian housewife who registered at the Clinic first in December, 1930. For a year and a half before her admission she had had increasing menorrhagia, and this had culminated in a profuse vaginal hemorrhage two weeks before her trip to the United States. She made no other complaints.

Physical examination, except that of the pelvis, gave negative results. Vaginal examination revealed a large carcinoma of the uterine cervix, which had extended into the anterior vaginal wall and into the broad ligament. The cervix was replaced by a huge crater. General laboratory examinations disclosed only mild secondary anemia and a few pus cells in the urinary sediment. In the next three weeks she was given a total of 6,597 mg. hrs. of radium, supplemented by a course of five roentgen treatments, over the front and back of the pelvic region. There was

*Presented at the meeting of General Staff, July 31, 1935. This paper is the first of two contributions by Dr. Walters, under the same general title. The second paper, which will deal with plastic operations on the urethra, will be published in an early issue.

INTRAVENOUS ANESTHESIA: PRELIMINARY REPORT OF THE USE OF TWO NEW THIOBARBITURATES

J. S. Lundy, M. D., Section on Anesthesia: Increase in use of intravenous anesthesia has been delayed because of lack of a suitable agent, but at times when a general anesthetic is needed the intravenous method is the best; for example, if the cautery or diathermy is to be used, and thus an inflammable agent would be dangerous, or if portability is of importance. For intravenous anesthesia the barbiturates, particularly, have been employed.[1, 2]

A barbiturate that was used intravenously about 1929 and several years thereafter was sodium amytal (fig. 1).[3] Figure 2, has been presented elsewhere, and its legend explains it. Sodium amytal has a prolonged effect. It is useful for intravenous administration in medical conditions such as convulsions, strychnine poisoning, eclampsia of pregnancy, gastric crisis, and certain manic conditions. Certain insane individuals respond sufficiently to sodium amytal to answer questions, or to be controlled for transportation. This agent is useful, also, in transportation of wounded persons. The drug, given intravenously, has been of value in emergency conditions, especially when a prolonged effect was desired and when the necessity was sufficient to justify its use. Its use for surgical anesthesia has been reported on previously, but it is justifiable to use it thus only occasionally.

The next step forward was the use of the isomer (fig. 3) of amytal, which was first called "embutal."[4] The sodium salt was called "nembutal" and finally, "pentobarbital sodium." This drug is about twice as potent as sodium amytal; therefore half as much could be used, recovery taking place in about half the time that was required when sodium amytal was employed. Pentobarbital sodium, when given intravenously in anesthetic doses, in emergency cases, was equally as valuable as sodium amytal except that, although the effect was sustained it was not as prolonged as that of sodium amytal. However, these drugs were found applicable when only small doses were needed and almost always it was possible to give small doses orally in sufficient time for the drug to be absorbed. Finally it was unnecessary to give them intravenously except, as I said, in occasional emergencies.

---

1. Lundy, J. S.: The barbiturates as anesthetics, hypnotics and antispasmodics: their use in 1000 surgical and nonsurgical cases in man and in operations on animals. Proc. Staff Meet. Mayo Clinic, 4: 225-228 (July 24) 1929.
   The use of barbituric acids, acetylene, spinal anesthesia, tribromethyl alcohol and other anesthetics in The Mayo Clinic in 1929. Minnesota Med. 13: 223-228 (April) 1930.
   Intravenous anesthesia: particularly hypnotic, anesthesia and toxic effects of certain new derivatives of barbituric acid. Current Res. Anesth. and Anal. 9: 210-217 (Sept.-Oct.) 1930.
2. Lundy, J. S. and Dixon, C. F.: The use of several new derivatives of barbituric acid. Minnesota Med. 13: 679-681 (Oct.) 1930.
3. Shonle, H. A. and Moment, A.: Some new hypnotics of the barbituric acid series. Jour. Am. Chem. Soc. 45: 243-249 (Jan.) 1923.
4. Fitch, R. H., Waters, R. M., and Tatum, A. L.: The intravenous use of the barbituric acid hypnotics in surgery Am. Jour. Surg. 9: 110-114 (July) 1930.

The barbiturates made the patient oblivious of the anesthetic and the operation, and a long period of sleep followed operation when sodium amytal had been used. Induction was very short; usually blood pressure was reduced, which tended to reduce bleeding, and depression of respiration rendered breathing quiet. The restlessness that followed operation in approximately 25 per cent of cases, and the long period of unconsciousness that frequently supervened were undesirable, particularly when it was doubtful whether the unconsciousness was attributable to the anesthetic, to intracranial hemorrhage, or to sudden increase in blood urea.

It was stressed by others, and by me, that pentobarbital sodium was different from the other barbiturates in common use in that it was a relatively shorter acting drug. Then, still shorter acting barbiturates were sought, and most of what follows will deal with three of them.

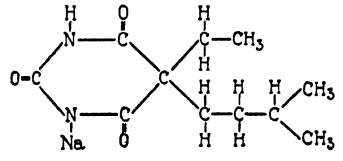

Fig. 1. Chemical structure of sodium amytal.

One of the new barbiturates, which appeared two or three years ago, is one of the shortest acting of them. It has been used in a large number of operations. This drug (sodium n-methyl-cyclohexenyl methyl malonyl urea) was introduced in Europe as "evipan" and in this country as "evipal soluble" (fig. 4).[5] It induces anesthesia quickly, respiration is quiet, and blood pressure is somewhat reduced, but the patient is seldom restless when he awakes and the period of recovery is short. This drug is on the market, and although fatalities have been reported from its use, it has seemed to me that these fatalities came about through failure to administer it properly. Occasionally reports appear that relaxation has been unsatisfactory, and muscular spasm often has been noted, especially in the period of induction.

In 1934, we of the Section on Anesthesia began to use a still newer type of barbiturate, sodium ethyl 1-methyl butyl thiobarbituric acid, employment[6] of which was attended by fair relaxation, short anesthesia, quick recovery, and absence of restlessness in almost all cases.[7, 8] With the exception that oxygen is replaced by sulphur (fig. 5), this agent is the same as pentobarbital sodium. This drug is approximately 33 to 50 per cent stronger than sodium n-methyl-cyclohexenyl methyl malonyl urea. It comes in an ampule together with a companion ampule of sterile, distilled water. The solution used is 10 per cent, and must be clear. A holder for round bottomed ampules can be devised, as is shown in figure 6.

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5. Weese, H. and Scharpff, W.: Evipan, ein neuartiges Einschlafmittel. Deutsch. med. Wchnschr. 58: 1205-1207 (July 29) 1932.
6. This is the drug referred to as "barbiturate A" in the "Annual report for 1934 of the Section on Anesthesia: including data on blood transfusion," which appeared in the "Proceedings of the Staff Meetings of the Mayo Clinic," 10: 257-272 (April 24) 1935. The name "thionembutal" was used in a paper by Lundy and Tovell, entitled "Some of the newer local and general anesthetic agents: methods of their administration," which appeared in "Northwest Medicine," 33: 308-311 (Sept.) 1934, and in a paper by Lundy, entitled "Usefulness of anesthetic agents in clinical practice," which is in press in the Canadian Medical Association Journal, where it is referred to as "thionembutal."
7. Lundy, J. S. and Tovell, R. M.: Annual report for 1934 of the Section on Anesthesia: including data on blood transfusion. Proc. Staff Meet. Mayo Clinic, 10: 257-272 (April 24) 1935.
8. Tabern, D. L. and Volwiler, E. H.: Sulphur-containing barbituric hypnotics. Unpublished data.

Another barbiturate, sodium allyl secondary butyl thiobarbituric acid, (fig. 7), referred to elsewhere as "barbiturate B," has been used in a few cases with results similar to those obtained with sodium ethyl 1-methyl butyl thiobarbituric acid. To avoid the long chemical names, I shall revert to terms used elsewhere and already mentioned in this paper; thus, sodium ethyl 1-methyl butyl thiobarbituric acid will be called barbiturate A and sodium allyl secondary butyl thiobarbituric acid will be called barbiturate B. Although barbiturate B is less potent than barbiturate A, it is about as potent as sodium-n-methyl-cyclohexenyl methyl malonyl urea. I have

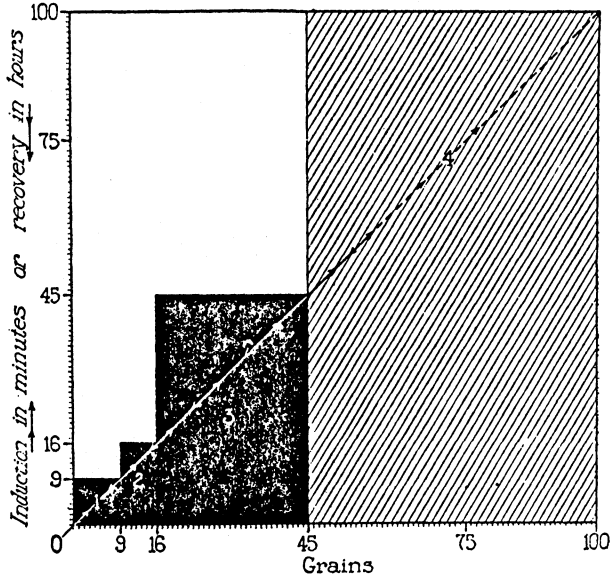

Fig. 2. A schematic presentation of the stages in the effect of sodium amytal given intravenously, showing the relationship between the dosage and effect in the average healthy adult. The scale has a triple meaning. If one is thinking in terms of dosage, the scale may be read in grains; if one is thinking of induction, the scale should be read in minutes (the maximal time used for producing the effect); if in terms of recovery, the scale should be read in hours. The figures within the black, or shaded, area, indicate the stage of effect of the barbiturate. First is the stage of hypnotic effect, the second the stage of inebriation, the third the stage of anesthesia, and the fourth, the premortem stage from overdose. Obviously but a small percentage of patients recover from the fourth, or premortem stage, if an overdose has been given. Induction is frequently hastened to but a fraction of the time indicated.

preferred barbiturate A to barbiturate B in surgical cases for the same reason that I prefer pentobarbital sodium to sodium amytal for surgical cases; I wish to use a minimal amount of drug to produce a given effect, anticipating that, at least in the average patient, the effect will be characteristic and that in the unusual case fewer variations will be noted than if a larger quantity of another drug had been given.

The method of giving barbiturate A and barbiturate B resembles that used in giving sodium n-methyl-cyclohexenyl methyl malonyl urea. An empty stomach is desirable, if not essential, and if the patient has material in the stomach, it should be emptied. To administer barbiturate A safely, the dose is two-thirds to a half as much as the dose of sodium n-methyl-cyclohexenyl methyl malonyl urea. The first curve (fig. 8) represents the depression of respiration associated with the quick, intravenous adminis-

tration of a safe dose of sodium n-methyl-cyclohexenyl methyl malonyl urea or of barbiturate A. The airway must be patent. Respiration may be depressed, and it is not sufficient to see respiratory movements; there must be evidence of respiratory exchange. We put a wisp of cotton over the nose and mouth and observe its motion. On injection of 3 grains (0.2 gm.), let us say, of sodium n-methyl-cyclohexenyl methyl malonyl urea respiration is depressed. If no more is administered, the patient recovers quickly and the depth of respiration increases. If 6 grains (0.4 gm.) is administered under the same conditions, respiration probably will stop temporarily, but the dose is a nonfatal overdose. On the other hand, if as much as perhaps 10 or 15 grains (0.65 or 1 gm.) is administered, respiration will stop and if artificial respiration is inadequate, this overdose will be fatal. To use this agent in the presence of bronchiectasis or of any other condition in which dyspnea or any respiratory obstruction exists is contraindicated, for the symptoms from the already existing condition will be aggravated by the drug. For example, in operations such as those in the upper part of the abdomen, traction on viscera may tend to interfere with respiration. If respiration is depressed so that anoxemia is apparent, the anesthetist should adequately ventilate the patient with oxygen, thereby largely eliminating one of the principal difficulties that may attend use of this method. In some operations an airway must be provided by a Magill intratracheal tube. This requires that the throat be treated with some surface anesthetic, as has been explained in other papers. After anesthesia has appeared following the first dose, the patient should be allowed to ventilate himself again and to show slight signs of return to consciousness or of response to painful stimuli. At that point, if sodium n-methyl-cyclohexenyl methyl malonyl urea is being used, a dose of 2 grains (0.12 gm.) may be administered intravenously; the needle is left in the vein throughout the operation. The second injection probably will give a longer period of anesthesia than the first one. At least it is evident, after injection of these two doses, how the patient will respond to the drug; it is possible to estimate the amount of drug that must be given at one time to re-anesthetize the patient. The whole amount of the drug is given in divided doses, much as when ether is administered by the drop method. All the ether needed for a long operation is not given at once; the same holds here. If respiration is deep, anesthesia is light. The period of inebriation that will follow administration of sodium n-methyl-cyclohexenyl methyl malonyl urea in the average case will last proportionately longer as more and more of the drug is given.

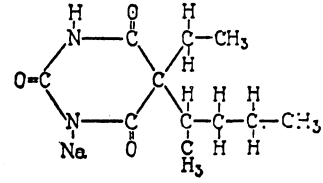

Fig. 3. Chemical structure of pentobarbital sodium

Certain additional hints will help in using these drugs. Since they are short-acting hypnotics they may be used for simple operations on ambulatory patients. Such patients should be able to walk without staggering before they are allowed to go home; for such recovery, from one to three hours may be necessary. In any case a friend should accompany the

patient much as though his inebriation were alcoholic. If a vein in the ankle of a patient with varicose veins is being used, after 1 or 2 c.c. of solution has been injected the vein should be massaged from the ankle toward the knee. Otherwise, in the presence of large varicose veins it is possible almost to empty the syringe before getting a noticeable systemic effect, but when the effect comes it will be extreme, from the large amount of drug injected. Since the individual who injects the drug cannot at the same time support the chin and maintain a free airway, I have found administration of this drug to be somewhat complicated, and since success in use of these new agents depends on their intermittent administration and constant attention to the intravenous injection, at present only experienced individuals should use them. In a few instances, accidental injection outside of the vein has occurred, but we have had only one case in which any destruction of tissue was evident. Some patients have complained of mild tenderness over the course of the vein used for injection. One case of marked phlebitis has been noted. I am undecided as to whether this tenderness of the vein is attributable to the drug, to trauma by the needle or to the probable injection of another drug in the same vein. Intramuscular administration of these agents has not been attempted. Probably these drugs will be more useful in institutions than where all facilities for their administration may not be available.

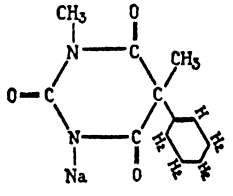

Fig. 4. Chemical structure of sodium n-methyl-cyclohexenyl methyl malonyl urea.

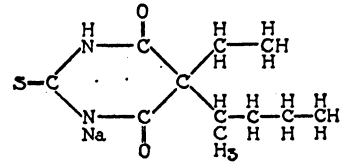

Fig. 5. Chemical structure of sodium ethyl 1-methyl butyl thiobarbituric acid (barbiturate A.)

The advantage of these short-acting barbiturates over other general anesthetics, and over certain local anesthetics, is in proportion to the brevity of the operation. Operations or painful procedures, especially minor ones, lasting up to ten or fifteen minutes, are satisfactory fields for these drugs. For ambulatory patients undergoing distinctly minor operations, local anesthesia may be preferred. If the operation is of longer duration or is a major one, it is only in special cases that these short-acting agents are particularly useful. For example, barbiturate A has been used satisfactorily to produce anesthesia for three and a half hours in a case of brain tumor complicated by pulmonary tuberculosis. Although 34½ grains (2.27 gm.) were given there were no ill effects. A Magill intratracheal tube provided an airway; it also furnished a means of artificial ventilation, and of administering an anesthetic by inhalation if these had become necessary. Both barbiturate A and sodium n-methyl-cyclohexenyl methyl malonyl urea are useful in small doses to produce unconsciousness for induction of anesthesia by inhalation, particularly if patients have facial defects. Short-acting barbiturates are indi-

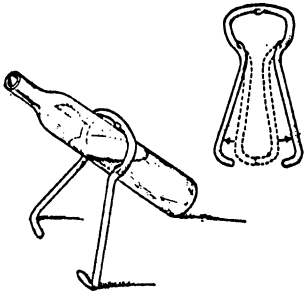

Fig. 6. A holder for round bottomed ampules.

cated for intravenous administration to control convulsions induced by local anesthetics.

I have found it advantageous to give morphine hypodermically and pentobarbital sodium by mouth, in small doses, to adults preliminary to administration of sodium n-methyl-cyclohexenyl methyl malonyl urea. With barbiturate A it is less important to give preliminary medication because of the increased potency of the drug. On the other hand, less of either drug will be needed if preliminary medication has been given than if it has not been given. Some patients who have had morphine, pentobarbital sodium and atrophine as medication before administration of barbiturate A, have awakened in the course of the operations, have given no evidence of pain at the time, have answered questions, and have had no memory of either pain or questions afterward. In each instance the answers seemed truthful. Perhaps this suggests a method for obtaining information from insane persons or criminals. The maintenance of analgesia in the presence of return of consciousness was not noted in all cases in which preliminary medication had been given but was never noted unless preliminary medication had been given.

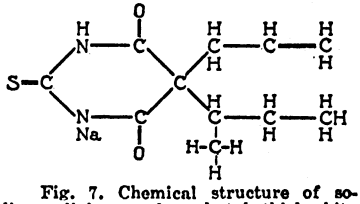

Fig. 7. Chemical structure of sodium allyl secondary butyl thiobarbituric acid (barbiturate B.)

Table 1
700 cases in which barbiturate A was used intravenously*

Occasions for use of the preparation	Cases
Operations on brain and other parts of central nervous system	24
Operation on eye	51
Dental extraction	27
Cystoscopic examination	137
Transurethral prostatic resection	20
Fulguration (bladder, urethra, and so forth)	31
Manipulation ureteral stone	16
Miscellaneous urologic procedures	47
Operation on ear	2
Operation within the thorax	20
Operation on breast	51
Operations on thoracic wall	12
Oral and plastic operations	80
Dilatation and curettage	50
Miscellaneous extra-abdominal operations	64
Miscellaneous intra-abdominal operations†	16
Spinal puncture	17
Removal of pack, drain and so forth	23
Dressing, insertion of radium, examination and so forth	12
Total	700

*Figures complete to August 23, 1935.
†Diverticulectomy, examination of region of gallbladder, incision and drainage of appendiceal abscess, appendectomy (3 cases), abdominal exploration (3 cases), repair of postoperative ventral hernia (2 cases), closure of colonic stoma (2 cases), right salpingectomy and removal of ovarian tumor, drainage of suprapubic abscess, secondary closure of abdominal wound.

These short-acting barbiturates may be given by mouth to induce sleep, but they do not replace pentobarbital sodium as medication preliminary to anesthesia. This is also true of another barbiturate, sodium propylmethyl-carbinyl-allyl barbiturate (seconal),[9,10] which, in the small series

9. Shonle, H. A.: Barbituric acids containing a secondary amyl group. Jour. Am. Chem Soc. 56: 2490-2491 (Nov.) 1934.
10. Shonle, H. A. and Kleidered, E. C.: Mixed melting point curves of some dialkylbarbituric acids. Jour. Am. Chem. Soc. 56: 2489-2490 (Nov.) 1934.

of cases in which I have used it, in hot weather, is unique among the barbiturates in that it nauseates some people.

Of the 700 cases represented in table 1, muscular spasm, that reminded me of the nystagmus that often follows an inebriating dose of a barbiturate, was observed in two. In one case, during induction and whenever anesthesia became light, there developed a slow, rhythmic, semirotary motion of the forearms, similar to the motion one would make if a door knob were grasped and it were slowly given a half-turn back and forth. Possibly the cause of these motions is related to the cause of the nystagmus.

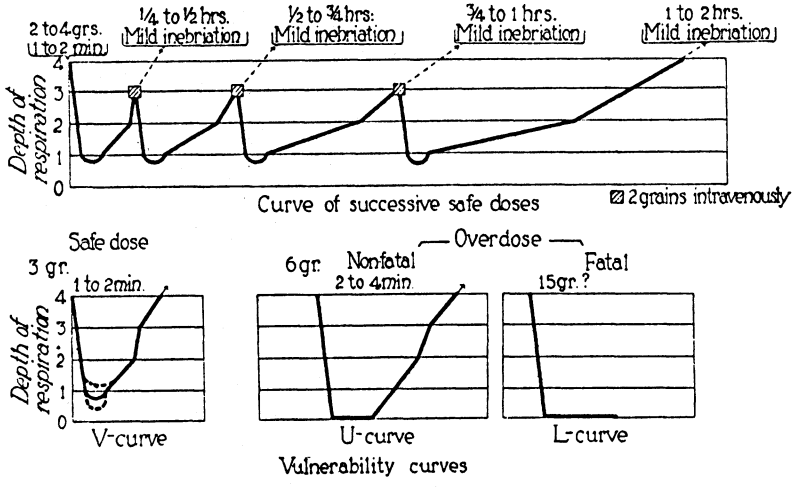

Fig. 8. The dose of sodium n-methyl-cyclohexenyl methyl malonyl urea intravenously for a man aged forty years, weighing 150 pounds (68 kg.); height 5½ feet; preliminary medication consisted of 1/6 grain (0.01 gm.) morphine by hypodermic injection and 1½ grain (0.087 gm.) pentobarbital sodium orally.

Effect produced by the administration of sodium n-methyl-cyclohexenyl methyl malonyl urea by different technics. The top curve gives the effect of repeated safe doses and needs to be further elaborated to fix the approximate duration of the effect of each dose. It illustrates the manner in which, when similar successive safe doses are given, the last one given has a longer effect than the previous ones. The curves, marked V, U and L, show the relative effect of the safe dose and of the overdose. The V curve illustrates the safe dose for the short operation, for example, simple extraction of a single tooth. The U curve illustrates the nonfatal result of a moderate overdose; respiration is practically completely depressed for a short time and the recovery is prompt if no more is given. It shows that the period of anesthesia is longer than when a small dose is given and this period of anesthesia is coincidental with respiratory depression. The overdose, that is, one large enough to be fatal, is illustrated in the L curve and needs no further explanation. Certain modifications of this technic might be carried out and the L curve could be broken down into two U curves the second of which might well be fatal, based on the results obtained in the top curve.

If the intravenous method is indicated for an intra-abdominal operation, anesthesia will be more successful if the surgeon is gentle. When relaxation must be obtained in repair of an incision, or in bronchoscopy, a local anesthetic also should be used. As I have pointed out before, this method occasionally makes possible some difficult procedures; for instance, a patient with a spastic condition, such as accompanies meningitis, may be placed in proper position for lumbar puncture. The applicability of these agents in urogenital surgery has been pointed out.[11] They have been used for operations about the thorax mostly when an inhalation anesthetic has been poorly tolerated previously, and especially when postoperative

11. Thompson, G. J.: Transurethral surgery in 1934. Proc. Staff Meet. Mayo Clinic, 10: 220-223 (April 3) 1935.

shock was anticipated. I have noted clinically, and there is some experimental evidence to indicate, that there is probably less postoperative shock following administration of a barbiturate intravenously than if drop ether alone has been used. As has been indicated, the drug is usable in dental surgery. When one or two teeth are to be extracted, preliminary medication need not be given. If several teeth are to be extracted, preliminary medication is advisable.

The ideal agent for routine intravenous anesthesia has not been found as yet but the available agents have been found to be satisfactory in certain types of cases.

CERTAIN MENSTRUAL DISTURBANCES ASSOCIATED WITH LOW BASAL METABOLIC RATES WITHOUT MYXEDEMA*

S. F. Haines, M. D., Division of Medicine, and R. D. Mussey, M. D., Section on Obstetrics and Gynecology: A group of seventy-four patients who had amenorrhea, oligomenorrhea, or menorrhagia, and low basal metabolic rates, but without signs of myxedema, were treated with carefully regulated oral doses of desiccated thyroid glands. Unnecessary complications of this treatment should be carefully avoided and this can be done only by careful observation and occasional determination of the basal metabolic rate for a few months, at least. Because of a desire to determine the effectiveness of desiccated thyroid alone in the treatment of these conditions, no patients who received any other form of treatment are included in the report.

Definite improvement in the menstrual flow was obtained in 72 per cent of the cases in which there was amenorrhea, in 55 per cent of the cases in which there was oligomenorrhea, and in 73 per cent of the cases in which there was menorrhagia. Aside from whether or not there was an improvement in the menstrual disturbance, about 75 per cent of the entire group of patients reported improvement in their general health after elevation of the basal metabolism to within the average normal limits.

*Presented at the meeting of the General Staff, July 31, 1935. Abstract of paper to be published elsewhere.