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Pre- and Post-Operative Management in Biliary Surgery

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THIS material is presented from a practical point of view, from the field of our actual practice. Our group is very fortunate in that, far from the madding crowd, we operate a small clinic and hospital under the same roof. All our working days are spent only a little distance away from our patients. We have to live with them during our waking hours and we have an opportunity to observe them, which has proved valuable.

Before dealing with the treatment of biliary surgery in particular, it would be well to deal with the subject of treatment in general. When we attend meetings and read the literature we occasionally get the idea that we must be creatures apart in the world of medicine. No one else seems to have trouble in persuading patients that they should be operated upon! No one else seems to have trouble in cutting the therapeutic cloak to the patient's financial cloth! We listen and read and wonder who pays the bill for all the fanciful measures in treatment and we wonder most of all where those patients come from who have money to pay for all the things recommended and yet have enough money left to pay the surgeon his reasonable fee. In our bitter experience those words “Spare no expense,” so frequently heard and so glibly uttered, have taught us to find out at once whose expense is being talked of because it has usually been ours in the end.

These difficulties, and the necessity of securing adequate results, have made us sift the wheat from the chaff in an endeavour to arrive at a rational and effective system of treatment. It is necessary that doctors concentrate upon diagnosis because without diagnosis there can be no rational treatment but we should not forget that to the patient treatment is the most important item and it is usually by our treatment results that we are judged. Without adequate treatment the patient thinks that diagnosis is but “sounding brass or a tinkling cymbal, and you may have the gift of prophecy in a disease and understand all its (Paper read at Mt. Carmel Mercy Hospital Clinic Day, Detroit, Mich., Jan. 31, 1940)
mysteries but if you cannot treat it efficiently you are to the patient nothing."

You will all agree that treatment means more than drugs, nursing, lights, and needles. You will probably agree that of all the major subjects taught in our medical schools today the subject of treatment is the most difficult to teach. In fact, most recent graduates have been taught to pay more attention to "treatments" rather than to the "art of treatment." This is a direct result of that age of therapeutic nihilism which had its inception with Virchow and reached its height with Osler, but there are indications that this age is passing.

Ryle is right when he says that we should be always learning that part of our Art which teaches when to order a shave for a male patient and a shampoo and curl for a female patient; when to order a bottle of beer or a glass of wine after meals; and when to order a change of room in a long illness. We should learn when to tease, when to joke, when to sympathize, when to bully and scold, and we should learn never to laugh at a patient.

The sifting of wheat from chaff in treatment recommendations should be conducted with two standards only in mind, the standards of Truth and Practicality. When these two standards are applied to the subject, fact will be found mixed with fancy, science with pseudo-science and common sense with nonsense in such proportions as to make all medical men ashamed and at times disgusted with the credulity of our profession. Lord Morley said that "An educated man knows when a thing is proved; and an educated man does not know." Our profession prides itself upon being scientific and yet we are so unskilled in the science of logic as to be unable to pick the good from the bad. Because of the want of logical thinking our patients are often compelled to pay for measures of little or no value.

We, the rank and file in the field of medicine, who have to deal with sick people and not with animals in laboratories, are not altogether to blame for this state of affairs. From our early days in medicine we are taught to bend the knee to the Goddess of Science and only too often our teachers and masters have forgotten that we should "enter the Temple of Science through the Portals of Doubt." "Medicine is not a science; it is an art which is trying to become a science," but by the time that hard knocks and bitter experience upon the firing line have taught us this truth it is often too late to achieve enough independence of judgment to "prove all things; hold fast that which is good."

We must retain our doubts. Like St. Thomas, we must ask for a sign, for proof, that we may believe. If we are afraid of criticism because of voicing our doubts we should remember that, in effect, St. Paul once asked "Am I then become a criminal because I speak the
truth?” And if St. Paul was stoned for telling the truth we should remember that his name lives today but no one knows the names of those who cast the stones.

I do not for a moment decry the immense benefits that scientific methods have brought to medicine. But all is not gold that glitters and all is not science that passes for science. If we examine this material with clinical sense and logical reasoning we shall find that great structures are built up on slender hypotheses and the end-results blind us to the shaky and even false beginnings.

It has recently been written that there should be a closed season on medical authors.3 There is such a flood of literature that no one man can swim in it. Fortunately it is not necessary because a large proportion of it is valueless. Once when I asked my old teacher what I should read to be medically saved he took me to the library and showed me the vast array of weeklies, monthlies, quarterlies, annuals, and textbooks and said “If all that were true no one would ever die!”

We have a duty to our patients. We must see that what we give them is the best possible treatment and only that which is necessary. If patients want anything else let them find quacks and let us save our dignity and self-respect. We should learn that it is possible to do many things to patients without doing anything for them. The sensible people, the people we enjoy dealing with, the people who pay their bills will understand and compliment us for giving them measures which actually work, measures which improve their well-being. Such measures can be arrived at only if we use logical reasoning based upon an adequate knowledge of the fundamentals. We are too often reading the “latest thing” on such and such a subject when our ground work of anatomy, physiology and pathology needs the time spent upon it.

You will agree with me that treatment should be based upon anatomical and physiological facts of the parts concerned. If facts are lacking and theories and hypotheses have to be used we should not forget the basis upon which we are building. Let us see how this applies to the pre- and post-operative management of biliary disease.

Nature does not seem to have made her mind up about the gall-bladder. In fact, there seems to be neither rhyme nor reason about it since it is present in some and absent in other members of the same species. Why, in the herbivora, should it be present in the cow and absent in the horse and deer? Why should it be present in most rodents and absent in the white rat? Why should it be present in most birds and absent in the pigeon? Excision of the gall-bladder certainly does not seem to hinder the efficient functioning of our patients.

What is the function of the gall-bladder? In the textbooks there are long and detailed expositions on the subject and the companies who
make bile salt medicinals furnish beautifully illustrated pamphlets on
the biliary function. But try to prove the statements in the texts and
in the pamphlets! Is the bile a secretion or an excretion? This appar­
etly simple question is unanswered. A liter of bile is said to be formed
daily and it is said that this is concentrated in the gall-bladder but the
gall-bladder only holds about one ounce. If you will think of the thin
gall-bladder walls, of the small artery and veins supplying it, and the
paucity of lymphatics you will wonder how all that fluid discarded in
the concentration is carried away.

It has been said that when the concentrated bile from the gall-
bladder is released and rushes forth to the duodenum it is again diluted
to its original volume by fluid secreted by the cells lining the biliary
ducts. However, if you open the duodenum to probe the lower portion
of the cystic duct and gently squeeze the one ounce gall-bladder to make
it empty you will not see several ounces pour forth and history does
not record that Kocher, who introduced this manoeuvre, was ever horri­
fied at getting ten for one? Perhaps the surgeon’s hand lacks the gentle
touch that Nature gives!

The actual function of the gall-bladder is as unknown as is that
of the spleen. There is a story that a clinician at the bedside asked one
of his students to tell him the function of the spleen. The student
looked at the ceiling, scratched his head, shuffled his feet, and replied
that he had known the function but had forgotten it. “My goodness,”
exclaimed the clinician, “what a loss to medical science. The only
man who ever knew the function of the spleen has forgotten it.”

Since science offers few facts, the treatment in biliary surgery, as
in all other treatment, depends largely on clinical sense and logical
reasoning. But because these cannot be weighed, or measured, or incu­
bated, or photographed do not despise them. They are two of the most
important items in the kit bag of the rank and file. Because they are
difficult to learn, and more difficult to impart, they should be likened
to rare jewels that everyone would be glad to own.

An uncritical survey of the literature would give the impression
that most cases of biliary surgery are complicated and difficult things
to manage. Experience teaches that this is not so and cases may be
divided into the following classes:

A—PRE-OPERATIVE

1. ORDINARY CASES. These comprise 88 per cent of the total and they
require no special management. They should enter hospital the day
before operation and they should have full diet up to the night before
operation. If the bowels have not moved on the day of entering hospital
an enema of normal saline may be given. A good night’s sleep should
be ensured and two drams of Elixir Bromochloral Compound is very
efficient. The less fussing done means a smoother subsequent course.
2. FEBRILE CASES \textit{(acute involvement)}. These comprise four per cent of cases and are subdivided into:

(a) \textit{Without Jaundice}. Treat these as ordinary cases and operate. If at operation adhesions are absent, or are light, remove the gall-bladder. If the adhesions are dense, numerous, and tough, drain the gall-bladder. This is a better course than waiting because we cannot see what is going on in the abdomen. Though a second operation may be required to remove the viscus later on "there are many things worse than a second operation and one of them is a funeral." We can deal only with that which is brought to us; we cannot have patients come to us in the optimum conditions we desire.

(b) \textit{With Jaundice}. Treat as outlined below.

3. JAUNDICED CASES. These comprise eight per cent of the total, and jaundice should be regarded as a definite indication for operation as soon as possible (excluding, of course, the catarrhal variety). The longer the jaundice lasts the greater the damage to the liver. Proceed as follows:

(a) Hospitalize the patient and estimate the "prothrombin" clotting time by Smith's easy, simple bedside test, 0.1 cc. Thromboplastin solution is placed in a test tube and the patient's blood added (from the vein) to 1 cc. Invert the tube to mix and begin counting seconds. Tilt the tube every few seconds to read clotting. The end point of the test is quite sharp and definite, hence mistakes are difficult to make. The normal clotting time by this method is 25 to 35 seconds with an average time of 30 seconds. A check is obtained by repeating the test using normal blood from a relative. The normal's time divided by the patient's time and multiplied by 100 gives a percentage. Bleeding is common at 40 per cent; the danger zone of bleeding lies between 40 per cent and 70 per cent; and with figures over 70 per cent bleeding is unusual.

(b) If the clotting time percentage is 70 per cent or over and the patient is not dehydrated, operate as an ordinary case. The question of dehydration is answered by the clinical examination of the tongue, the skin, the brightness of the sclerae, and the amount of urine passed in the preceding 24 hours.

(c) If the clotting time is unsatisfactory there are two methods at our disposal:

(i) The best, simplest, and safest according to the admittedly present unsatisfactory state of our knowledge seems to lie in the use of Methyl-naphthaquinone solution intramuscularly (Glaxo Laboratories). This chemical seems to be the active portion of the so-called vitamin K and is used by giving two ampoules of five mgm. each intramuscularly on the first day of treatment followed by five mgm. daily for three or four days. The clotting time often shows improvement within
24 hours and operation may usually be performed by the fourth day but treatment by using five mgm. daily may be continued until satisfactory improvement in the clotting time is attained.

(ii) Less satisfactory because of retention and absorption difficulties is the use of vitamin K preparations such as Cerophyll in two-dram doses thrice daily, accompanied by ten grains of bile salts thrice daily. This method has not been very satisfactory in our hands but more experience is needed. The literature on vitamin K must be read with a great deal of reserve; the whole matter is highly theoretical and there are many possible fallacies. We must not be too enthusiastic and we should prepare for disappointments. To those who object to this view, I would reply that fifteen years ago calcium was the answer to the treatment of the jaundiced patient. Scores of articles were written proving the benefits of calcium and the theory that calcium in the blood united with the bile acids to prevent clotting of the blood! Remember, for example, that the very subject of clotting of blood is still in the theory stage and that there are two rival views.

(d) If the patient is dehydrated, urge the oral intake of fruit juice drinks sweetened to taste. If the patient does not drink, or drinks and does not retain the fluids, a rectal drip of half strength normal saline solution given at the rate of about 20 drops per minute should be used. It is more reasonable to expect the absorption of a hypotonic solution than an isotonic solution, hence the use of half strength normal saline. If the intravenous use of fluids is deemed necessary one or two liters of five or ten per cent glucose in normal saline may be given. Larger amounts than this are never necessary.

Much has been written on the fluid requirements of the surgical patient and various estimates have been made of the amount required. 3,500 cc. daily seems to be the favourite figure and while I cannot follow the reasoning given for this figure I do know from a personal experiment that 3,500 cc. of fluid is an embarrassing and uncomfortable amount to dispose of. The amount becomes the more fearsome when it is translated into the more familiar figures of only a few ounces less than a gallon.

It will be pertinent to point out at this juncture that in a collected series of 4,000 operations performed upon jaundiced patients in Europe and America that about 13 per cent died. Of these deaths about 14 per cent were attributed to haemorrhage due to the jaundice (61 patients). Res ipsa loquitur!

Before dealing with the post-operative treatment it is necessary to mention a few points on the operation itself which make after-care so much simpler. The main incision should be closed and drainage, which should be carried out in all cases, performed through a separate stab
wound. We remove the gall-bladder where it lies; we have given up rotating the liver and the surgeon's hand should not be passed between the liver and the diaphragm as is sometimes advised. The incision is a straight one, dividing the rectus muscle, and must reach the costal margin above. We use no mechanical spreading retractors in the wound. The best retractor is the assistant's hand over the towels used to pack off the viscera and the next best is a Harrington's spring-handled retractor. One retractor in the wound is sufficient whether it be a hand or an instrument.

**B—POST-OPERATIVE**

1. **SIMPLE CASES.**

   (a) Nurse the patient with the head and trunk slightly elevated to take the tension off the wound and thus make deep breathing easier.

   (b) Encourage the taking of several deep breaths several times daily. Many of these patients are fat and flabby and do not breathe deeply unless taught to do so. After operations on the upper abdomen there is a reflex inhibition which tends to prevent adequate ventilation of the lower lung lobes and voluntary efforts at deep breathing will tend to overcome this feature.

   (c) Bandage the patient lightly. All that is necessary over the main wound is a light dressing and the drain and tab wound can be dressed separately. Dressing changes can then be performed with comfort to the patient.

   (d) Give adequate doses of morphine hypodermically to keep the patient comfortable but with each dose of morphine give ¼ grain of atropine. The atropine depresses the vagus and thereby aids in preventing vomiting and tends to relax the pylorus and sphincter of Oddi. It also keeps the patient from sweating and losing water through the skin and by increasing thirst persuades the patient to drink more fluids. The effects of atropine upon the air passages seem to be beneficial in preventing the inspiration of mucus into the pulmonary alveoli.

   (e) Give water and juice drinks in small amounts and frequently. We are satisfied with any intake of a liter or over in 24 hours. We often use the rectal drip mentioned previously but rarely find it necessary or advisable to give intravenous fluids. When intravenous fluids are used we rarely give more than a liter of glucose and saline in 24 hours. Protein, like fat, stimulates the flow of bile into the intestine and when given as a gelatin preparation it is relished by most patients as it is tasty and cold. Fats early in the post-operative stage are repulsive to most patients and milk is often “gasy.” Soft diet is ordered as soon as possible and when full diet is ordered a little snack is given in the afternoon and at bedtime to encourage the biliary tract to empty itself.

   (f) On the third post-operative day give one ounce of castor oil
followed by a normal saline enema in four hours if no evacuation has occurred. After clinical experimentation with other laxatives we have returned to castor oil as being the best. If the patient simply cannot take castor oil use Milk of Magnesia in ounce doses thrice daily until an evacuation occurs.

2. Complicated Cases.

(a) Pneumonia. Sulphapyradine is given in effective doses and continued long enough until all danger of recrudescence is passed. Digitalis is given only if fibrillation occurs and then it is given in full doses. Routine administration of digitalis in pneumonia is probably a hindrance rather than a help. In the words of Sir James Barr, "Digitalis is useless when the heart is in the grip of a toxin."

(b) Haemorrhage due to oozing may be controlled by further administration of methyl-naphthaquinone or vitamin K as outlined previously. Small blood transfusions of between 300 and 500 cc. may be used but in our opinion blood transfusions are done too frequently and unnecessarily. The pendulum has swung from venesection to the putting in of blood in the last century and neither extreme is correct.

(c) Sepsis. In the event of wound sepsis remove the stitches early to give free exit to pus and prevent tissue damage. We leave the drain placed through the stab wound in situ for seven days before shortening it and it is completely removed about the tenth day.

(d) Cardiovascular. If the heart was good enough to begin with and the surgery rapid and gentle this is an uncommon complication. If trouble does occur digitalis and oxygen are the stand-bys. Embolism as a complication is unpredictable, unpreventable, and for all practical purposes untreatable.

(e) Vomiting beginning after the second day should always raise the question of stomach dilatation. We allow one vomit and after that the nasal tube is passed, the stomach washed out, and siphonage begun by allowing the free end of the nasal tube to lie below the level of the patient. If necessary, we elevate the foot of the bed and turn the patient on to the right side.

It will be seen that in this schema of treatment ordinary common-sense measures are mainly used and that there is an absence of frills, especially the expensive frills. The complaint of expensive medical care is often justified and the blame lies at the doctor's door. Results obtained justify continuing the use of the schema outlined and we hope the experience of others will be as satisfactory as ours.

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The Estimation of the Relative Concentrations of the Phosphatases in Bone

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The phosphatases constitute a large group of esterases whose functions are to catalyze the hydrolysis of phosphoric acid esters, that is to say, compounds such as the phosphoric acid esters of the fats, proteins and carbohydrates and the nucleic acids. These enzymes are present in virtually all living matter so far investigated and take part in certain physiological processes involving the metabolism of fats, proteins, carbohydrates and phosphorus; lactation, reproduction, ossification and calcification, as well as muscular contraction and fermentation.

Of the phosphatases, the most important with respect to the metabolism of bone are, first, the alkaline phosphatases, the optimal reaction for the activity of which lies between pH 8 and pH 10 depending upon the substrate and, secondly, the acid phosphatases for which the optimal pH is between four and six.

The alkaline phosphatase system is complex. The enzyme itself appears to be composed of protein molecules with molecular weights from 6,000 to 10,000. It is a mixture of molecular species, separable into at least two fractions. In this regard, Bamann and Salzer (1938) in their recent work refer to the lyo- and desmo-enzymes. According to their views, there are three classes of enzymes. The endo-enzymes such as the yeast carbohydrases are imbedded in or adsorbed on the cell walls so that, while actually soluble, they are prevented from going into solution and are not extractable from the cells by water or glycerine. But, after the mechanical destruction of the cells, the enzymes are liberated and pass into solution. The desmo-enzymes are those which are bound to the protoplasm by chemical bonds and are insoluble, therefore, until their “carrier” is broken down into smaller, soluble protein molecules. For this reason, the desmo-phosphatase produces an active aqueous extract on autolysis of the tissue in which it occurs. The resulting “carrier molecules” are of various molecular weights, but the specifically active group is the same in all of them and remains unchanged during the different transitions. There is no sharp dividing line between the endo- and desmo-enzymes. The lyo-enzymes are ecto-
enzymes, or freely secreted enzymes and they pass readily through the cell walls and circulate, for instance, in the blood stream. Also, they are easily and rapidly extractable from the tissues by water or glycerine. The lyo-enzymes occur naturally in a freely soluble state, although actually the decomposed desmo-enzymes may approximate the lyo-enzymes as regards their properties. The lyo-enzyme and the desmo-enzyme groups thus merge into one another. The lyo-enzymes are marked by a very great tendency toward activation; for example, the lyo-phosphatase is activated as much as 5,000 per cent by magnesium ions, while the desmo-phosphatase is activated but slightly in this manner. Methods are available for the separation and study of the lyo- and desmo-phosphatases.

Cloetens (1939a) based his belief in the existence of two different enzyme species upon the chemical behaviour of extracts. It has been known for many years that magnesium ions activate the alkaline phosphatases (Erdman, 1928). These are true activators in the sense that they increase the velocity with which the hydrolysis of the substrate begins. Also, potassium cyanide inhibits alkaline phosphatase activity. Therefore, on the basis of the results obtained by measuring the phosphatase activity in the presence and the absence of these reagents, he postulated the existence of two enzyme species whose behaviour was different. Phosphatase I is defined as that which is inactive in the absence of 1/100 M. MgSO₄ and at the same time is not influenced by 1/100 M. KCN. Phosphatase II is that which is active in the absence of MgSO₄ and is completely inhibited by 1/100 M. KCN. Cloetens calculated the percentage of each type of phosphatase in typical extracts of animal tissues by measuring the activity of the extracts with combinations of the above-mentioned reagents in different concentrations. While the phosphatase of the rat’s intestine consists only up to two per cent of phosphatase I and rat’s bones about four per cent, the kidney contains about 14 per cent and the liver about 90 per cent of this fraction. An intestinal phosphatase extract gave results indicating that the enzyme was about 100 per cent phosphatase II and a fraction of the liver phosphatase precipitated during dialysis was obtained which was apparently 100 per cent phosphatase I.

Subsequently, Cloetens (1939b) reported the separation of the alkaline phosphatase I from the liver phosphatases by successive inactivation of the alkaline phosphatase II and the acid phosphatases. He studied the properties of this separated phosphatase I. It exhibited greater stability in acid medium, lack of activity in acid medium, marked inhibition by fluorides and stabilization in alkaline medium by magnesium ions. It may be seen, therefore, that the phosphatase I bears a close relationship to the lyo-enzyme; probably the identity of the two fractions may be established.
A third method of differentiation of the enzyme species is implied in O. Bodansky's (1937) work on the effect of the bile acids on the alkaline phosphatase extracts of various organs. He concluded that the phosphatases of bone, blood serum and kidney were identical in that they were inhibited about 50 per cent by 0.00625 M. bile acids, while intestinal phosphatase was affected only very slightly, if at all, by bile acids. Possibly this difference is due to the presence of two or more molecular species, one of which is inhibited by the bile acids and the species may be present in different proportions to yield the observed results. However, as yet there is no indication that such an opinion is true, since the two species have not been separated further than the implication contained in the statement that intestinal phosphatase must consist almost entirely of one variety. There are no general relationships between these methods of differentiation and no other physical or chemical observations have suggested the possibility of the presence of different molecular species.

In those experiments reported in the literature which were carried out under conditions in which the optimal concentration of magnesium ions was not used, the phosphatase activities would be variable depending upon the concentrations of magnesium which were present. While the results so obtained would be reproducible for a given extract, they would not be valid for comparing extracts in which the magnesium concentration might differ. For this reason, it is better to dialize the extracts free from magnesium and then add the optimal amount of this substance to the hydrolysis mixture. The proper concentration is about 1/100 M. in the final solution.

With this optimal concentration of magnesium ions, the phosphatase activity is the sum of the lyo-enzyme, fully activated, plus the desmo-enzyme liberated by the autolysis, activated to its slight extent, or the phosphatase activity is the sum of phosphatase I, fully activated, and phosphatase II activated to its fullest extent. The results then are not only reproducible for a given extract, but they are also comparable with those obtained with other extracts because the total activities of fully activated enzymes are compared.

Under optimal conditions of pH and magnesium ion concentration, the graph expressing the amount of phosphate liberated as a function of time is linear for the first one per cent of the hydrolysis of the substrate present. After that, the rate of hydrolysis falls off as the products of hydrolysis inhibit the enzyme. For this one per cent, the reaction is of zero order and the reaction velocity is proportional to the concentration of the enzyme. O. Bodansky (1936) found that the presence of an optimal concentration of alpha-amino acids prevented the inactivation of the enzyme by the hydrolysis products until ten per
One percent of the substrate had been hydrolyzed, thus extending the range over which the reaction was of zero order from one per cent to ten per cent of the hydrolysis. This made the initial reaction velocity, which is proportional to the concentration of the enzyme, much easier to determine because of the greater changes in time and the amount of phosphate liberated. Thus, for accurate work, the extracts are dialyzed free of alpha-amino acids and sufficient glycine, the simplest alpha-amino acid, is added to bring the final concentration of the acid in the hydrolysis mixture to \(0.00625\, \text{M}\), which is the optimal concentration for glycine. Each alpha-amino acid possesses its own optimal concentration, which in general is lower for those of higher molecular weight.

The acid phosphatases with their optima between pH 4 and pH 6 have not been investigated to the same extent as the alkaline phosphatases, but these also are complex substances (Baman and Salzer, 1938). They are composed of two enzyme species, one having an optimal pH of five decimal five and the other pH four. No activators or compounds which prevent the inactivation of the enzyme by the hydrolysis products have been reported. The reaction is of zero order for the first ten per cent of the hydrolysis of the substrate without further addition (Lundsteen and Vermehren, 1939).

To measure the relative concentrations of the enzymes in the bones, it is necessary to extract them as completely as possible. This is done by a routine procedure so that the extraction will be the same in all cases. The method which is employed is essentially that of Mardland and Robison (1929). The bones of the rats, after being cleaned thoroughly, are broken into small fragments. These fragments may be extracted directly or they may be ground up, using an accurately weighed amount of sand or ground glass in the process. Then the broken or ground bones are autolyzed for two days (or other standard period of time) in five or ten times their weight of sterile water, to which is added 1 cc. of toluene for each 10 cc. of water. The autolysis is carried out at room temperature because the inactivation of the enzyme is small and the extraction is rapid at this temperature.

The autolyzed bones are filtered and the filtrate is collected in a collodion membrane in which it is allowed to dialize for about 36 hours at room temperature against a 20-fold volume of distilled water changed at least every 12 hours. This will remove most of the phosphate ions, most of the alpha-amino acids and will bring about the decomposition of phosphoric acid esters which may interfere in the subsequent estimation of the phosphatase activity of the extracts. The dialysate is removed, diluted to a definite volume and stored in a refrigerator with a few drops of toluene added as a preservative.

If, for any reason, the extracts must be kept for some time, it is preferable to remove the enzyme in the form of a powder. Instead of
diluting the dialysate to a definite volume, it is dried to a powder in an evacuated desiccator over concentrated sulphuric acid. No loss of activity occurs with this treatment. Dialysis may be eliminated by precipitating the enzyme from the filtrate by the method of Martland and Robison (1929). They use a twofold volume of alcohol and a threefold volume of ether for each volume of filtrate. The precipitate forms rapidly and is easily filtered off and dried. The dry powder stored in a refrigerator is active for a long time and is readily dispersible in water when it is necessary to estimate its activity. The method of Albers and Albers (1935) may also be used. Extraneous protein is removed by bringing the extract to an alcohol content of 50 per cent. The enzyme is soluble under these conditions while much of the inactive protein is not. Then the alcohol content is raised to about 70 per cent and the enzyme is precipitated, filtered off and dried. In both of these methods, the enzyme is separated from inorganic phosphates and alpha-amino acids, and in the latter method it is separated from much of the protein as well. Some loss of activity may occur, however, by the use of these methods.

The bony fragments which have been filtered off are extracted fat-free by ether. This can be done very conveniently in a Bailey-Walker extractor. The residue is then dried at 110°C for a short time and weighed, subtracting, if necessary, the weight of any added sand or glass. The bone then is heated to determine the amount of ash and protein present.

The most satisfactory method of expressing the phosphatase activity of bone is by a measure of the reaction velocity of the hydrolysis of the substrate. The method for the alkaline phosphatase is that of O. Bodansky (1937) in which the substrate is sodium beta-glycerophosphate, the optimal concentration being 0.0127 M. The hydrolysis of this substrate is carried out in a pyrex glass-stoppered test tube in a final volume of eight cc. Thus to obtain the correct concentration, one cc. of 0.1016 M. sodium beta-glycerophosphate is used in the eight cc. This substrate, on hydrolysis, produces glycerine which does not inhibit the enzyme and phosphoric acid which does inhibit the enzyme when present in large concentrations. It is the phosphate which is estimated chemically as a means of following the reaction.

The desirability of comparing phosphatase activities at the optimal pH for the enzyme is generally recognized. The range of pH for optimal action is narrow (9.0 to 9.2) and the slopes of the pH-activity curve on either side of the optimum are steep. To insure that the determinations are conducted at the optimal pH, a series of hydrolyses, constituting in effect a very closely spaced pH-activity curve in and about the optimal range, is run for each determination. The pH of the hydrolysis
solution is brought to the neighborhood of the optimum by the use of sodium diethyl barbiturate (sodium veronal) as a buffer, in a concentration of 0.5 per cent obtained by adding 0.4 cc. of a ten per cent solution as a part of the 8 cc. of the hydrolysis mixture. In order to vary the reaction, a dilute solution of sodium hydroxide (0.2 N.) is added to four or more of the reaction mixtures in amounts varying from 0.0 to 0.3 cc. or more. In this way, each succeeding reaction vessel is at a slightly higher pH than the preceding one. The vessel at the optimal pH is chosen when the amount of phosphate liberated in each is estimated. The vessel in which the greatest amount of phosphate has been liberated in a given time is the one which has been at the optimal pH. Usually, at least one such reaction vessel is found in four parallel determinations, but sometimes the amounts of alkali must be increased, or if the mixtures are already too alkaline, replaced by 0.2 N. HCl. This sensitivity to pH changes makes the method laborious in that four parallel hydrolyses must be carried out, only one of which is actually used in the final calculations.

Magnesium chloride to give the optimal concentration of magnesium ions is added, 0.1 cc. of a molar solution, giving a final concentration in the reaction mixture of 0.0125 M. Glycine to give a final concentration of 0.00625 M. is added also (0.1 cc of a 0.5 M. solution). Then the total volume of eight cc. is completed with distilled water and the dialized phosphatase extract. Hydrolysis of the substrate is carried out at 25°C in a constant temperature water-bath thermostatically controlled. The reaction is started by adding the enzyme extract and the time noted. Then at intervals chosen so that the times are about equally spaced over the first ten per cent hydrolysis of the substrate, aliquot portions, usually one cc., of the mixture are withdrawn and added to five cc. of a ten per cent solution of trichloracetic acid. For a well dialized and not too active phosphatase extract, no precipitate will form which interferes with the estimation of the phosphate. If a precipitate is likely to form, the trichloracetic acid solution is increased to seven cc. and the aliquot of the reaction mixture added to this. Then the precipitated protein is filtered off, using a No. 44 Whatman filter paper, and six cc. of the filtrate is used for the estimation of the phosphate. Under such conditions, a correction must be applied to take care of the phosphate lost in the filtering, that is, the final six cc. contains only three-quarters of the phosphate contained in the original one cc. aliquot of the hydrolysis mixture. The trichloracetic acid stops the hydrolysis by destroying the activity of the enzyme and, further, it does not promote the hydrolysis of the substrate. Therefore, inactivated aliquots may be stored overnight in a refrigerator without fear of the phosphate content being changed.

The phosphate in the aliquots is estimated colorimetrically by the modified Kuttner-Lichtenstein method (A. Bodansky, 1937). The six cc.
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composed of the aliquot from the hydrolysis mixture and the five cc. of trichloracetic acid solution are treated first with the molybdic acid solution made up according to the directions given by Bodansky, then with a stannous chloride solution. The phosphate ions catalyze the reduction of the molybdic acid to the blue-coloured hydrous oxide. The number of molecules of molybdic acid reduced is a function of the reduction potential, but for stannous chloride in the concentration used, there are nine reduced for each phosphate ion present. Equilibrium is reached in a few minutes at the most, but it is best to leave the mixture for from one-half to one hour, especially if much trichloracetic acid is present and if the solutions are cold. The colour is stable for at least two hours. Since the colour is proportional to the number of phosphate ions present, under the same experimental conditions, the phosphate concentration is obtained by comparison with a standard of known concentration. In the use of an ordinary visual colorimeter, the intensity of the colour varies widely from direct proportionality to the length of the column so that corrections for deviations from Beer's law must be applied. Also, the solution must be normal in respect to hydrogen ion concentration so that, in the presence of trichloracetic acid which changes the pH, corrections for this must be made. Furthermore, the small concentration of sodium beta-glycerophosphate present affects the intensity of the colour developed. Tables, corrected for deviations from Beer's law to be applied to the comparison of standards and tables corrected for the deviations from Beer's law and for the presence of the usual concentrations of sodium beta-glycerophosphate and trichloracetic acid applied to the comparison of the unknown samples with the standards have been calculated by Bodansky for use in serum phosphatase determinations. These may be converted to use with the above methods of hydrolysis by appropriate factors.

The four values for the phosphate calculated on the basis of the phosphate content per cc. of the hydrolysis solution, that is, the actual phosphate content of the one cc. aliquots removed from the hydrolysis mixture, are plotted against the time the reaction has proceeded. If the hydrolysis has not exceeded 10 per cent of the substrate and optimal conditions have existed, the graph will be a straight line. Then the reaction velocity may be measured legitimately by the amount of substrate hydrolyzed in a given time. However, this is not always a certain method since the hydrolysis may exceed ten per cent of the substrate. If, during the first ten per cent, the curve is linear, then the hydrolysis has occurred under optimal conditions and hence the time-change function is the same as that for all such hydrolyses occurring under optimal conditions. For this reason, the best measure of the reaction velocity is the $Q_{0.05}$ which represent the reciprocal of the time necessary for the hydrolysis to liberate 0.05 mgm. of phosphorus in the form of the phos-
phate from the substrate per cc. of the hydrolysis mixture. When the hydrolysis is carried out under optimal conditions, this measure of the reaction velocity will be proportional to the concentration of the enzyme present and, conversely, if a definite quantity of tissue is used to prepare a definite volume of extract, it will be a measure of the relative concentration of the enzyme in the tissue.

To determine the activity of the acid phosphatases, the same procedure is used except that the buffer is different. Acetic acid and sodium acetate are added to give a final concentration of 1/20 M. for each. This is accomplished best by adding 0.4 cc. of a solution molar in respect to each. Since this buffer has a great capacity and, since pH changes are not as critical for the acid phosphatase as for the alkaline phosphatase, only the one estimation need be run for each extract. In this case again the measure of the reaction velocity is proportional to the concentration of the enzyme and, conversely, it is a measure of the relative concentrations of the enzyme in the tissues if a definite weight of that tissue yields a definite volume of extract.

In this manner, the relative concentrations of the enzymes in the tissues are expressable as a measure of the reaction velocity \( Q_{0.05} \) per some constituent or function of the tissues. For instance, the relative concentrations might be expressed as the phosphatase activity per gram of bone. This is not absolutely precise because of the variable content of water and fat in the bone. The phosphatase activity per gram of fat-free bone is more exact. Roche, Filippi and Leandri (1937) expressed their results as the phosphatase activity per mgm. of nitrogen in the bone but I suggest the activity per gram of protein in the dry, fat-free bone. Both methods are based upon the observation that the phosphatasic activity of the bone is associated with the development of its protein content. Not any of these means of expressing the phosphatase activity of tissues are entirely satisfactory, in that all the reference constituents of the bones are capable of wide variations which may mask fluctuations in the concentration of the phosphatases.

In general, by obtaining a measure of the reaction velocity of the hydrolysis of a substrate in the presence of an aliquot portion of a known volume of phosphatase extract derived from bone of which the exact weight of a constituent is known, then the reaction velocity per gram of that constituent will be a measure of the relative concentrations of the enzymes in the bone. If the extract is always diluted to the same volume and the same volume of aliquot is used, then a simple factor will convert the measured reaction velocity to the reaction velocity which would be obtained if all the extract were used and this, divided by the weight of the reference constituent of the bone, will be the relative activity, or the relative concentration of the enzymes in the bone. While it must be admitted that this method gives only the
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variations in the total fully-activated activity of the phosphatases as a function of a constituent of the bone which may vary, nevertheless, this method appears to be the most satisfactory so far developed. It would seem that no constituent of the bones is so constant that it can be accepted as an infallible reference material.

The extraction of the phosphatases is the most uncertain step in the procedure and so must be carried out with the utmost uniformity. Subsequent handling of the extract must be done with care also to prevent loss of the enzyme. But losses will be small in the usual careful analytical procedures. The actual determinations of the reaction velocity of the aliquot of the extract may be carried out with an accuracy of about two per cent. While no definite value can be placed on the accuracy of the entire procedure, I believe that it is definitely more accurate than the less tedious but more uncertain methods employed heretofore.

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The History of Artificial Pneumothorax

By G. H. C. Joynt, M.D.
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Although artificial pneumothorax has become one of our everyday procedures in the treatment of pulmonary tuberculosis, it is of interest to know that the idea of inducing a collapse of a tuberculous lung was conceived a great many years ago. Some mention of the injection of air into the chest as an aid in the treatment of disease of the lung (probably empyema) was made in the treatise “On Affections” of the Hippocratic Collection which dates back to the fourth century before Christ. Sporadic reports of incision of the chest in patients with pulmonary tuberculosis have appeared from the sixteenth century onward. In these reports no clear distinction was made between drainage of the pleural cavity and collapse of the lung. Until Laennec discovered auscultation in 1816 the diagnosis and treatment of disease of the lungs made but little progress.

Early in the nineteenth century specific suggestions for the collapse of a tuberculous lung were first recorded. Historically, England leads the way. In 1821 J. Carson, a physiologist of Liverpool, reported that animals recovered easily from artificially induced pneumothorax and concluded that collapse of the lung suppressing its elasticity would be a secure, simple and complete remedy for suppurative lesions or of cavities of the organ. Carson in 1822 recommended the induction of pneumothorax in two cases of advanced pulmonary tuberculosis. The procedure was carried out by a Liverpool surgeon, Bickersteth, in the presence of Carson. An incision was made through the pleura to the lung but no pneumothorax was produced, due to adhesions. At autopsy the pleura was found to be adherent in both cases.

Although these attempts were unsuccessful, it is undeniable that Carson’s reasoning and deduction based upon experimental evidence was correct. In his famous book Carson stated, “It has long been my opinion that if ever this disease is cured, and it is an event of which I am by no means disposed in all cases to despair, it must be accomplished by mechanical means or, in other words, by a surgical operation.” It was only the unfortunate choice of subjects that prevented Carson from making an epoch-making discovery which was to be done fifty years later by Forlanini.

Carson’s work fell into oblivion and collapse therapy had a long period of preparation and development. In 1832 Houghton reported improvement in a case of advanced phthisis as the result of a spontaneous pneumothorax. Stokes, a contemporary of Houghton, described in the Dublin Journal of Medical Science the beneficial effect of spon-
taneous pneumothorax in pulmonary tuberculosis. In 1834 Ramadge of England reported favourable results with thoracentesis in pulmonary tuberculosis but his views did not attract the attention of the profession. But in the middle of the nineteenth century the opinion seemed to prevail that tuberculous pneumothorax was always fatal. Potain of France studied the problem of curative pneumothorax and in his teaching constantly referred to the possibility of curing phthisis by artificial pneumothorax. Toussaint, a pupil of Potain, in 1880, set forth on clinical grounds the claims of pulmonary collapse. He reported the beneficial effects of spontaneous pneumothorax and pleural effusion in certain cases of pulmonary tuberculosis. Hérad, in 1881, made the observation that pneumothorax did not always kill a tuberculous patient but might favour healing.

During the period between Carson (1821) and Forlanini (1882) the work of Laennec, Pasteur, and Lister laid a foundation for the establishment of pneumothorax therapy. Carlo Forlanini of Pavia, Italy, in his first, now famous, paper published from Milan in 1882 suggested the use of artificial pneumothorax in the treatment of pulmonary tuberculosis. Forlanini meticulously gathered together all the unassembled pertinent facts on pneumothorax and appeared to be particularly interested in Toussaint's report of cases benefited by spontaneous pneumothorax. Forlanini proposed to immobilize the lung permanently and pointed out that artificial pneumothorax was the best way. In his article almost all the fundamentals of pneumothorax were described but he lacked a technique and did not understand selective collapse although he did predict selective re-expansion. It was not until 1888 that Forlanini, after experimenting with animals, first injected air into a pleural effusion, in a case of one-sided phthisis. Four years later, in 1892, he first produced an artificial pneumothorax in a patient with pulmonary tuberculosis and in 1894, in Rome, he reported his first two cases of artificial pneumothorax. Forlanini advocated the gradual induction of pulmonary collapse with frequent refills of small amounts of nitrogen. Most of Forlanini's cases were hopeless and he concluded that "the curative results were only meagre." As a result nobody felt encouraged to follow his example and his work was practically unknown outside of Italy.

Between Forlanini's first and second reports, Cayley of England, in 1885, attempted to cure a case of severe haemoptysis by making an incision in the chest and creating a pneumothorax. The haemorrhage was controlled but the patient died of sepsis. In the discussion of Cayley's paper Parker recommended aseptic precautions and the injection of filtered and carbolized air into the pleura. Adams, in England (1887), and Spath, in Germany (1888), reported the possibility of treating phthisis with artificial pneumothorax and proposed to carry this thought into practice. In 1888 Potain, in France, who
preceded Forlanini by several years in the application of pneumothorax in the treatment of pleural effusions, published his work on the replacements of effusions with sterilized air in three tuberculous patients with spontaneous hydropneumothorax. His first case was successfully treated in 1885. Potain used a manometer to accurately measure intrapleural pressure and he also studied absorption of various gases, finally concluding that nitrogen was the least readily absorbed. He also pointed out the benefits of prolonging the collapse of a tuberculous lung and his therapeutic results were good but he found no followers.

In America, Murphy, a Chicago surgeon, apparently unaware of Forlanini's work, reported in 1898 a series of eight cases (five in detail) of pulmonary tuberculosis which were treated with artificial pneumothorax. He was unsuccessful with three cases, due to adhesions, but did treat five patients with injections of nitrogen gas in amounts varying from 1155 to 3300 cc. Murphy, in contrast to Forlanini, advised the injection of very large amounts of nitrogen with refills at intervals of six to ten weeks. He suggested that the lung should remain collapsed for three to six months. Probably Murphy's greatest contribution to pneumothorax therapy was his emphasis on the use of X-ray in the control of pulmonary collapse. Murphy, in 1898, was the first to publish prints of roentgenograms of lungs collapsed by pneumothorax. This was only three years after Roentgen's discovery of the X-ray and at that time the average exposure of plates was thirty to seventy seconds, as compared with one-tenth of a second today.

Murphy did not continue with pneumothorax therapy and dropped the procedure soon after his original essay. He turned over this work to his associate, Lemke, who began using the Murphy technique. In 1898 Lemke reported the use of artificial pneumothorax in 53 cases, one of which was the first recorded case of alternate compression of the lungs. In 1902 Lemke published a report of over 350 cases of pulmonary tuberculosis treated by pneumothorax.

Only a few reports of artificial pneumothorax were published in America from 1902 until 1912, at which time artificial pneumothorax was generally adopted on this continent. Schell of Indiana described a case in 1898 in which he resorted to artificial pneumothorax to control a case of haemoptysis. Young also in 1898 published a report of treatment of pulmonary tuberculosis by artificial pneumothorax. In 1900, Loomis of New York reported the use of artificial pneumothorax in eighteen cases of pulmonary tuberculosis. In this series, eight cases of haemoptysis were treated with good results.

Meanwhile in Europe a renaissance in collapse therapy had begun. Brauer of Germany, attracted by the work of Murphy and Lemke, began to take a keen interest in pneumothorax therapy. In December 1905 he reported his first case of artificial pneumothorax and shortly
after he published the report of a second case. At this time (1906) Forlanini, who had kept silent on his work with pulmonary collapse, claimed a priority in the invention of artificial pneumothorax. Forlanini gave an account of twenty-five cases of pulmonary tuberculosis which he had treated with pneumothorax from 1894 to 1906 and briefly described his technique. Nevertheless, it is of interest to know that Brauer obtained his idea from Murphy and it was through Brauer’s work that collapse therapy became a rational and methodical procedure. Brauer first used Murphy’s technique of creating a voluminous pneumothorax at once but later adopted Forlanini’s method of frequent small refills. In 1906 Spengler in Switzerland and Schmidt in Germany also took up the use of artificial pneumothorax, using Brauer’s incision method.

Saugman, in Denmark, had made two unsuccessful attempts at artificial pneumothorax in 1902 and 1904 but in 1906 he again began treatment and was successful in a number of cases. Saugman’s great contribution was the addition of a manometer to the pneumothorax apparatus which gave the technique a degree of safety. Not until this time were the tools for pneumothorax complete and it remained for subsequent workers to refine the technique.

In 1909 Dumarest, after learning the technique of pneumothorax from Forlanini, revived this procedure in France. Shortly after Kuss and Rist, also of France, began the use of artificial pneumothorax in the treatment of pulmonary tuberculosis. Almost simultaneously pneumothorax therapy was taken up by Muralt in Switzerland, Thue, Mjoen and Holmboe in Norway, and Delprat in Holland. Ascoli at the International Tuberculosis Congress at Rome in 1912 reported the first case of pulmonary tuberculosis treated bilaterally with pneumothorax.

The general adoption of pneumothorax therapy in the United States began with the work of Robinson and Floyd in Boston. It was Pratt of Boston who, after reading the published papers of Brauer and Schmidt, persuaded Robinson on January 24, 1909, to do a pneumothorax for him on a case of pulmonary tuberculosis. The following September Robinson and Floyd began their work in a tent ward at the Massachusetts General Hospital. In April, 1912, they published a series of twenty-eight cases.

Balboni, also of Boston, began the use of artificial pneumothorax in 1911. Lapham of North Carolina introduced collapse therapy in the South and between 1910 and 1913 published nine reports of artificial pneumothorax. In 1911 Minor and Ringer in Asheville began pneumothorax treatments.

Lillingston and Colebrook re-introduced pneumothorax therapy to the country of Carson and Cayley. Lillingston pointed out that English
pneumothorax patients in Switzerland were unable in the summer of 1910 to return to England due to the inability of any physician to continue the treatment. In August, 1910, Lillingston produced a pneumothorax in a patient at Mundesley Sanatorium. Colebrook, a pupil of Lillingston, began the use of pneumothorax therapy in 1911.

In Canada, the treatment was early undertaken by several physicians in Ontario. On December 16, 1898, Rogers of Ingersoll first used artificial pneumothorax in a far advanced case of pulmonary tuberculosis. Two refills were given but the patient died about six months after the start of pneumothorax. In 1899 Rogers started pneumothorax on two other patients but due to the poor results in these far advanced cases he became discouraged with the treatment and discontinued it. In 1900 artificial pneumothorax was simultaneously taken up by Third of Kingston and MacKinnon of Guelph. In 1912 MacKinnon reported five cases using Murphy's method. In 1903 Third read a paper on pneumothorax therapy but did not mention case reports until 1918, when he reported in an unpublished paper the treatment of fifty-one cases with artificial pneumothorax.

The general adoption of artificial pneumothorax in Canada began in 1913 and 1914 and the first paper on pneumothorax therapy in Canada was read in April, 1914, before the Toronto Academy of Medicine by Parffit and Crombie. This report included twenty-four cases in which pneumothorax had been attempted. In three cases of this series no pneumothorax was obtained. In addition to this they had also produced partial compression in six patients with pleural effusion by the replacement of the fluid with air or nitrogen. Their first case of artificial pneumothorax was started on December 18th, 1912, at Calydor Sanatorium, Gravenhurst. This patient had advanced pulmonary tuberculosis with great displacement of the heart to the left but a good pneumothorax was obtained. After five years' experience with pneumothorax therapy Parffitt and Crombie published a report of their first sixty-three cases of pulmonary tuberculosis in which pneumothorax was induced, between December, 1912, and December, 1917. Their first forty-nine cases were chosen, and the early punctures made without the help of the X-ray. Fluoroscopy and X-rays were used in six of these cases at later dates. The patients were carefully examined before and after treatments and particular note was made of the position of the apex beat. The initial pneumothorax was given with oxygen to avoid air embolism and subsequent refills were given with nitrogen.

At the Muskoka Hospital, Gravenhurst, the first pneumothorax was started in April, 1914, by Kendall and this patient is still living and well. In 1925 Kendall reported 331 cases of artificial pneumothorax started at Muskoka Hospital from 1914 to March, 1925. Kendall was assisted in his work by Hazlewood. In early cases at Muskoka Hospital
oxygen was used for the initial pneumothorax and refills were given with nitrogen.

The first pneumothorax started at the Queen Alexandra Sanatorium, London, was done by Craig on March 30, 1917. A complete collapse was obtained but the patient subsequently died six and a half years later from disease in the opposite lung. The second case, a fifty-one year old man, was started by Craig on August 6, 1917. A good collapse was obtained and he was discharged from sanatorium on June 21, 1918. This patient returned to work in 1919 and pneumothorax therapy was eventually discontinued on April 23, 1927. In the first case 700 cc. of air was given on the initial pneumothorax and refills of 1000 to 1250 cc. of air were given at various intervals. Subsequent pneumothorax therapy at the Queen Alexandra Sanatorium was done by Ferguson and Campbell.

Most of the pioneers in collapse therapy used nitrogen gas for the maintenance of artificial pneumothorax because it was advocated as the gas least readily absorbed from the pleural cavity. In 1912 Haldane, the Oxford physiologist, expressed the opinion that nitrogen could have little, if any, advantage over the use of air, because in either case diffusion of gases would rapidly occur. In 1914 Webb, Gilbert, James and Havens analyzed the gas in a series of pneumothorax cases and concluded that there was little advantage, if any, to be gained by the employment of nitrogen rather than atmospheric air for the production of artificial pneumothorax. Since that time air has been chiefly used in the production and maintenance of artificial pneumothorax.

The different methods originally advocated for producing pneumothorax are those of the three pioneers of the field. Forlanini adopted the puncture method (thoracentesis) with a small aspirating needle. Originally no manometer was used and the point of the needle was determined largely by art or by the free entry of gas into the pleural cavity. Forlanini’s communicating bottles were not movable and the gas was displaced by water subjected to pressure produced by means of a rubber bulb.

Murphy originated a very similar method. The skin was first punctured with a tenotomy knife and this produced an opening for a trocar with cannula to be easily introduced. The cannula was attached to a vessel containing nitrogen under hydrostatic pressure. The trocar was pushed inward and when the rib was reached the stilette was withdrawn and the trocar was then pushed through the parietal pleura. The gas under pressure was kept directly connected to the cannula during its passage through the chest wall and when the cannula was pushed through the parietal pleura the gas flowed freely unless the pleura was adherent. This original method obviously caused frequent air emboli.
This danger of air emboli led Brauer to employ the incision method (thoracotomy). This technique is often called the Murphy-Brauer method although Murphy's technique was essentially a simple puncture method. With the Brauer technique a five to seven centimeter incision was made in the skin and the underlying muscle and fascia layers exposing the parietal pleura. A blunt needle was then introduced through the exposed pleura. This procedure was done under local anaesthesia but there were many disadvantages including the much greater possibility of infection. The incision method was employed only at the first injection and refills were given with the ordinary aspirating needle.

With the addition of the manometer by Saugman to the pneumothorax apparatus the puncture method became more widely used and proved to be a simple and safe technique. Numerous special needles were introduced by various operators and many are still used. At the present time at the Queen Alexandra Sanatorium a plain, blunt needle is most frequently used for the initial pneumothorax. Thus the modern puncture method is essentially a modification of the technique of Forlanini and Murphy.

**SUMMARY**

The idea of inducing artificial pneumothorax for the treatment of pulmonary tuberculosis was conceived by a Liverpool physician, Carson, over a century ago. The application of pneumothorax therapy was carried out independently by Forlanini in Italy in 1894 and Murphy in America in 1898. In the subsequent clinical application Brauer's work added the impulse to artificial pneumothorax that made it a rational and methodical procedure. Spengler, Schmidt and Saugman, in Europe, made conspicuous contributions to pneumothorax therapy. In America, excellent articles by Floyd and Robinson, and Lapham in the United States, and by Parffit and Crombie in Canada, brought the procedure of artificial pneumothorax to the attention of the profession on this continent.

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WHAT EVERY WOMAN DOESN'T KNOW—HOW TO GIVE COD LIVER OIL

What Every Woman Doesn't Know is that psychology is more important than flavouring in persuading children to take cod liver oil. Some mothers fail to realize, so great is their own distaste for cod liver oil, that most babies will not only take the oil if properly given, but will actually enjoy it. Proof of this is seen in orphanages and pediatric hospitals where cod liver oil is administered as a food in a matter of fact manner, with the result that refusals are rarely encountered.

The mother who wrinkles her nose and "makes a face" of disgust as she measures out cod liver oil is almost certain to set the pattern for similar behaviour on the part of her baby.

Most babies can be taught to take the pure oil if, as Eliot points out, the mother looks on it with favour and no unpleasant associations are attached to it. If the mother herself takes some of the oil, the child is further encouraged.

The dose of cod liver oil may be followed by orange juice, but if administered at an early age, usually no vehicle is required. The oil should not be mixed with the milk or the cereal feeding unless allowance is made for the oil which clings to the bottle or the bowl.

On account of its higher potency in Vitamins A and D, Mead's Cod Liver Oil Fortified With Percomorph Liver Oil may be given in one-third the ordinary cod liver oil dosage, and is particularly desirable in cases of fat intolerance.
Burns and Their Treatment
By Irving Weintraub, '40

A BURN may be defined as the lesion resulting from the application
of a super-heated medium to the surface of the skin, the excessive
exposure of the skin to chemicals, electricity, ultraviolet rays or the
effects of radium and X-ray. When the heat effect is through a moist
or liquid medium, it is termed a scald.

CLASSIFICATION

It has been customary to describe a burn according to the depth
of the tissue destruction. Six degrees of tissue destruction are usually
described, but this is more of an histological classification than a prac­
tical one, so attempts to grade burns clinically have led to much con­
fusion. For practical purposes it is better to divide burns into three
degrees: first degree is reddening of the skin; second degree is blister
formation; third degree is total destruction of the true skin with or
without destruction of the underlying structures.

Goldblatt divides burns into two types only. Type one is a scarring
burn that will require special treatment to minimize the scar, and
type two is a non-scarring burn that will require no special treatment.

PROGNOSIS

The extent of a burn is more important than its depth insofar as
the prognosis is concerned, but the depth, extent and location of the
lesion are the important factors concerned in the treatment.

Certain authorities give the following prognostic signs: in adults,
first degree burns are fatal if two-thirds of the body surface is involved,
second degree burns are fatal if one-third of the body surface is
involved; in children, second degree burns are fatal if one-seventh of
the body surface is involved.

The body surface is divided so that the lower extremities, including
the buttocks, comprise two-fifths of the body surface, the trunk and
the neck together comprise another two-fifths, the upper extremities
and the head the remaining one-fifth.

SYMPTOMATOLOGY

It used to be thought that the absorption of decomposed proteins
was the explanation for the symptoms occurring after a burn, but as
a result of recent work, the clinical course of a patient with a severe
burn cannot be explained on the basis of any one theory. Clinically a
burn may be divided into four aspects:

(1) Initial shock of the injury itself.
(2) Concentration of the blood.
(3) Toxic reaction.
(4) Residual ulceration.
Initial Shock: The shock present with even small burns is identical with the clinical picture of traumatic or surgical shock and is characterized by loss of body heat, cold, moist skin, rapid pulse and a fall in blood pressure. This phase is usually transient but may be prolonged or fatal if not recognized and treated.

Concentration of the Blood: There occurs within a few hours of the burn a severe concentration of the blood. The haemoglobin may rise to over 200 per cent and a sustained haemoglobin of 140 per cent is incompatible with life. This concentration interferes with the normal functioning of the blood and eventually leads to suspension of vital processes. The N. P. N. is raised, the chlorides are lowered and the urinary output is diminished.

By forcing fluids during this period, the volume of blood and the cardiac function is brought back to normal, but this forcing of fluids should not be carried out too zealously without thought of the patient. Trusler and his associates found by experimental and clinical studies that in the usual treatment of severe burns, water intoxication was a complicating factor. This condition was first described by Roundtree in 1923 when he noticed a peculiar symptom complex in patients with diabetes insipidus who continued to drink huge quantities of water after the urinary output had been decreased by posterior pituitary solution. It is also similar to the condition found in firemen who drink a great deal of water while sweating, thus losing an excess of chlorides. Burned patients are thirsty because of fluid loss and drink a great deal of water.

Due to the stagnation of the circulation and the escape of blood plasma from the injured capillaries, there is a concentration of the blood with a great reduction in the chlorides. Intravenous saline does increase the chloride content but it does not remain in the capillaries; instead it washes the blood fluids into the tissue spaces, giving a still greater fall in the serum proteins.

Their "studies indicate that repeated transfusions of blood offer the only safe means of maintaining the blood chemical balance. There is also an indication that blood plasma alone should be given, as the red blood cells become excessive in number. When the blood fluid balance is safeguarded in this manner, other fluids may be given in moderate amounts."

Toxic Reaction: The toxemia corresponds roughly to the extent of the burn, appears one or several days after the injury and is ushered in by restlessness, steadily mounting fever, nausea and vomiting, which is often followed by delirium, convulsions and coma.

Many theories have been advanced concerning this toxic reaction. The first of these theories has to do with the loss of the skin functions
(heat regulation, elimination of wastes, sensation, etc.). Experiments have been performed to prove this theory, but the evidence is not convincing.

The most widely accepted theory at the present time seems to indicate that there is absorption of some unknown toxin formed from the burned tissue. It was thought that if this burned tissue could be coagulated, toxic absorption would be prevented. So in 1924 Davidson introduced the use of tannic acid, which precipitates the proteins. With the same idea in mind, Bettman applied silver nitrate after the tannic acid application to shorten the period of coagulation of the tissue proteins.

With the use of tannic acid there has been little decrease in the death rate from burns, and so in 1930 Underhill disproved this theory of toxic absorption to his satisfaction. He concluded from his investigations that the loss of body fluids and the consequent concentration of the blood are the factors responsible for death.

In 1933, Aldrich furnished bacteriological evidence that the toxemia resulting from the burn was in most cases due to secondary infection of the traumatized tissues. He was able to isolate gram positive beta-haemolytic streptococci from the area after twelve hours and in fatal cases obtained positive blood cultures of the same organism. Examination of the viscera showed evidence compatible with acute infection and sepsis. He introduced the use of one per cent aqueous solution of gentian violet because of its high bactericidal effect on the gram positive organisms and its escharotic value, but unfortunately it has little effect on the gram negative organisms. To overcome this failing, he recently introduced a compound consisting of brilliant green and acriviolet, the latter being a mixture of acriflavine and gentian violet.

On the basis of Aldrich's work, it would seem that sulphanilamide would be a natural adjuvant to the therapy of this phase, but as far as this writer was able to determine, it has not as yet been used.

All organs of the body may show pathological changes in cases of extensive cutaneous burns. Belt found in a number of cases of burns that the effect on the liver was similar to that observed in certain virus diseases, especially yellow fever, and suggests that the noxious agent may be of similar character.

Einhauser and others have shown that there is injury to the adrenal cortex with the passage of serum into the tissue spaces where it acts like a foreign protein. He called this process serous inflammation. Adrenal cortex hormone was administered to a few cases with some benefit, but experience with its use has been too inadequate for any definite conclusion to be drawn.
Gastro-intestinal ulceration following severe burns is associated with swelling and haemorrhage into the adrenals, the latter being a constant finding in fatal cases. A parallel to this is the fact that adrenalectomized dogs develop acute peptic ulcer. Kapinow believes the ulceration is due to a concentration of the blood and its consequent tendency to form thrombi as shown by the higher incidence of peptic ulcer in patients with polycythaemia vera. Haemoconcentration may be the explanation in the early stages of the burn, due to the loss of plasma. In the later stage, it may be due to adrenal damage which manifests itself by blood concentration.

**TREATMENT**

The treatment of burns varies from one clinic to the next, but one feature is common to all and that is a definite plan of action that must be rigidly adhered to whether the burn be severe or moderate. Regardless of the programme decided upon, it must:

1. Combat the initial shock.
2. Combat the fluid loss.
3. Prevent and treat the toxemia.
4. Promote healing and lessen the period of disability.
5. Prevent permanent deformity.

**Shock:** Shock is the first consideration and must be treated before local therapy is instituted. Meyer and Wilkey are of the opinion that all persons with one-eighth or more of burned body surface should be treated for shock whether it is present or not.

**Fluid Loss:** A burn involving one-sixth of the body surface may cause a loss of fluid in twenty-four hours that is equal to 70 per cent of the total blood volume. To replace the blood chlorides and bolster the liver, intravenous saline and glucose should be given as soon as possible. Subsequent need for fluid is determined by the haemoglobin concentration, the blood chloride and N. P. N. levels. The fluid intake and output should be recorded and blood transfusion given, especially in severe burns.

**Mild Burns:** In the first or small second degree burns, various substances are used with good results.

Picric acid in a one per cent solution is both analgesic and anti-septic, but it stains everything it comes in contact with.

Butesin picrate combines the anaesthetic properties of butesin with those of picric acid and is very valuable in the mild uninfected burns. All the blisters should be aseptically drained before application.

The tannic acid preparations are perhaps the most widely used because they are cleaner to use and are not a grease which would have to be removed if the burn were of a greater degree than first supposed.

Aluminum subacetate in a two to five per cent solution and amyl
salicylate mixed with dichloramine-T have been tried, but have no value superior to the above types of treatment.

Severe Burns: Meyer and Wilkey in a series of 968 burn cases at Cook County Hospital have evaluated the various methods used in their treatment of severe burns.

Tannic Acid: The patient is cleansed, debridement carried out and then placed on sterile sheets with a heat cradle. A five per cent aqueous solution of tannic acid is sprayed on every 15 minutes until a good eschar is formed. As the crust curls up it is cut away and if serum collects it is drained.

In 272 cases treated as above, 108 showed infection and 34 died, a mortality of 12.1 per cent.

Compound Aniline Dye: The area is cleaned by soft ether sponging only if grease or oils have been used. All blebs are opened aseptically, but no extensive debridement is attempted. The heat cradle is used and the area is sprayed every hour with the eschar forming in about eight hours. The crust has to be closely watched for infections, which show as a moist area. This area should then be excised and dried with sterile sponges and the dye reapplied. This procedure is continued until good granulations are formed. The disadvantage of its use is very evident, being a dye it stains everything it comes in contact with.

Of 104 cases of second and third degree burns treated in this manner, only ten became infected and nine died, a mortality of eight decimal seven per cent.

Gentian Violet: The burned area is cleaned and a debridement is done. The area is sprayed with one per cent gentian violet and covered with a cradle.

One hundred and twenty-five cases, consisting mainly of second degree burns of the extremeties, were treated by this method and 22 became infected and two died, a mortality of one decimal six per cent.

Tannic Acid-Silver Nitrate: All the grease and oil must be removed, so the area is cleaned with benzine and dried with the electric dryer. A five per cent solution of tannic acid is sprayed on and this is immediately followed by ten per cent silver nitrate, which is applied to the surface of the burn by cotton pledgets. A flexible crust forms in a few minutes, which is the great value of this method. If the crust loosens, it is removed and the area is treated with scarlet red.

Two hundred and twenty burns were so treated. Of these, 18 became infected and 19 died, a mortality of eight decimal six per cent, but the period of hospitalization was shortened and the scarring and deformities were minimized.
Methyl Rosaniline-Silver Nitrate: This treatment was advanced by Branch in 1937 and consists of applying ten per cent silver nitrate after thorough cleansing, thus forming a milky white coagulum. Methyl rosaniline stains the crust violet and aids in destroying and preventing infection. After spraying with a one per cent solution of the dye, the heat cradle is applied. The area is sprayed every fifteen minutes for five applications and then once a day as necessary. After two weeks the crust is soaked off by a warm sodium bicarbonate bath and scarlet red is applied. Skin grafts were not needed.

Twenty-six cases of second degree burns of the extremities were so treated with two infections and no deaths.

Cod Liver Oil: After cleansing with warm boric acid and a debridement, cod liver oil was applied to 38 cases of first and second degree burns. Good results were obtained in all the first degree burns, but of 26 second degree burns, eight became infected and healing was delayed in a great number. The fish odour was very disagreeable but there were no deaths.

Puestow and his associates showed experimentally that other oils containing Vitamins A and D were as efficacious as cod liver oil and that healing was about 25 per cent faster than with the controls treated by tannic acid and vitamin free oils.

Continuous Bath: This is of value in extensive second and third degree burns but is seldom used because of the special apparatus necessary and the need for constant supervision by a trained attendant. It is of special value when the patient is in coma with dyspnoea and anuria. It relieves pain, improves the circulation of the skin and helps prevent some of the toxic absorption. It is of value because no crusts form, the islands of epithelium are not destroyed, the wound is clean and healthy and skin grafting can be done much earlier. This method may be modified by placing the patient in the tub two or three times daily for one or two hours at a time and in the interim having the patient in bed with the burns covered with perforated cellophane which is covered by saline packs.

Severely Contaminated Burns: In contaminated burns and those over 12 hours old, where infection is assured, moist saline or boric dressings are applied three or four times per day and the burn is washed with white soap at each dressing. Xeroform strips, which are gauze impregnated with sterile vaseline and three per cent xeroform, are used and are changed daily, at each change the area being cleansed with boric acid and white soap. A sterile dressing is placed over the strips, then a sea sponge and all this is held in place by means of a binder. The sponge absorbs the secretions and is supposed to prevent the formation of excessive granulation tissue.
Of 186 cases thus treated there were two deaths, a mortality of decimal six per cent. The hospitalization is longer but the mortality is lower with this treatment and scarring and deformity are not excessive.

Aldrich recognizes the benefit of tannic acid if used before twenty-four hours or before infection is present and maintains that its value lay only in its early application with the subsequent sealing off of the burn by a sterile eschar, thus preventing infection. Opposed to this idea is Murless, who believes that there is no time limit after which tannic acid treatment should be abandoned and that good results may be obtained even with sepsis. His best results were obtained by covering the burned area with a mixture of five per cent methylene blue and one per cent brilliant green, and then spraying it with 20 per cent tannic acid in 1:1000 acriflavin. The area is dried with an electric dryer and resprayed every three hours for forty-eight hours. When pus forms under the eschar it is allowed to exude along the edges but the crust is not removed. A high fever is expected, which lasts two or three days, but there is no pain and the healing time is greatly reduced with a much better cosmetic result.

Infra-red Radiation: Gautier, working in France, recommends the use of infra-red radiations which are to be started while the lesion is being cleaned. It is claimed that the pain will subside within one-half hour, that healing is accomplished in a much shorter time and that the scars are supple, painless and reactionless. It can be used after any previous type of treatments and forms a protecting crust after three or four sittings of one hour each. In second degree burns, the epithelization is perfect but in third degree burns the results are not so good.

Tannic Acid Bath: For burns in children, Blackfield and Goldman advocate the use of the tannic acid bath because it combats shock, facilitates debridement, starts eschar formation and is a simple and easy method of applying tannic acid. They place the patient immediately into a bath of tannic acid kept at 90-100°F. and proceed with the debridement and cleansing of the skin. The tannic acid may be changed several times, depending on the amount of debridement necessary. After this has been completed, the patient is dried with a sterile towel and ten per cent silver nitrate is blotted over the burned area, producing an immediate crust and sealing the area before infection can take place. The entire area but especially the surrounding skin and crust edges are then treated with one per cent gentian violet three or four times a day to keep it free of organisms. The patient is kept on sterile sheets with a heat cradle.

After 7-14 days the edges of the eschar loosen and curl up and are then cut off and the area again painted with gentian violet. Spontaneous epithelization is assumed to occur within three weeks, so after this
length of time the crust is soaked off wherever possible and the rest of it is excised with the patient under a light anaesthesia. The burned area is then treated as a wound in preparation for grafting by the use of saline compresses and sodium hypochlorite.

**Surgical Intervention:** A modified debridement is carried out in nearly all the forms of treatment, but complete surgical excision of all the burned tissue under a general anaesthetic is not as yet advised as a routine procedure in severe deep burns.

The type of treatment depends on the depth of the burn. In second degree burns there are at least a few scattered deep-lying islands of epithelium remaining from which rather prompt coverage will occur without much deep scarring. The manner and course of healing is entirely different after total destruction of the skin. Repair occurs much later and, according to Blair and Byars, "is accomplished by three distinct but somewhat overlapping processes. First, the raw surface is gradually covered by granulations; second, the deeper and older layer of these granulations takes on the character of contracting scars, which draw in the surrounding skin and superficial fascia, thus lessening the actual surface area to be repaired; third, after some days, weeks, or months, earlier under proper treatment, epithelization of the remaining raw area starts with a visible ingrowth of the surrounding skin and perhaps from scattered epithelial remnants." The scar which forms may be keloid in type, very weak and thin and tends to break down or may develop a malignancy in later years.

Active surgical repair should be started as early as possible and aims at permanent skin coverage of all raw surfaces. This may be accomplished by using large split grafts or small pinch grafts that serve as foci for epithelization. Grafting is generally done on a patient in good condition but occasionally a simple graft is used to aid a poorly progressing patient. Homografts which are taken from the parent are generally used in this condition. They seldom last more than three weeks but tend to stimulate spontaneous epithelization and is often a life-saving measure.

Some of the most distressing conditions are seen following the improper care and treatment of burns. Blair and Byars state that "the chief point in the late correction of deformities is the liberation of false union and elimination of binding scars." This can usually be done by excising the scar areas down to their deepest elastic layer, immediate application of large split thickness skin grafts, full thickness grafts or a sliding or pedicle flap. There is little to be gained by the attempt to grow skin grafts on a granulating area of years duration without first removing the granulations and the underlying scar, which latter may be from a fourth to a half inch thick. Much late grief and multiple operations can be avoided by early successful skin coverage.
SUMMARY

This paper is an attempt to show the latest and most efficient methods for treating patients suffering burns and the rationale of the methods.

The most important factor in any type of treatment is the saving of life. This is accomplished by treating the shock and maintaining the water balance. To best preserve the latter, the haemoglobin, blood chlorides, blood N.P.N. and the fluid intake and output should be carefully watched.

As for the treatment of the burn itself, it seems that the tannic acid-silver nitrate method, whether the acid is sprayed on or used as a bath, is best for the non-infected cases. For the severely infected ones, the compound aniline dye or the use of moist saline dressings plus cleansing with white soap yield the best results. For those with complete destruction of the skin, a clean and suitable surface should be obtained as soon as possible so that a skin graft may be applied.

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Temperature Regulation and the Mechanism of Fever*

By Max Nareff, Meds '42

A proper understanding of fever, the general response of the body to an infection or injury, and its mechanisms, requires first a consideration of the temperature regulation under normal conditions.

Normal Temperature Regulation: The body temperature of man is a balance between two opposing processes, heat production and heat elimination.

(1) Heat Production: Heat is produced in the body as a result of exothermic chemical reactions occurring during rest and activity. The skeletal musculature, by virtue of its bulk, is the body's prime generator of heat. The glands also produce heat, in fact gram per gram, more than the muscle. The intake of food, particularly protein, causes increased heat production which is not due to digestive or absorptive activities. The food itself stimulates metabolism. This is known as the Specific Dynamic Action of protein and has as yet no satisfactory explanation. The thyroid and adrenal glands, by virtue of the calorigenic action of their secretions, play a large role in heat production. Cannon found that the secretion of adrenaline occurs on exposure to cold, which is probably an important mechanism in the body's reaction to cold.

The processes involved in increasing or decreasing heat production are referred to as the chemical regulation of body temperature. Exposure to cold causes increased heat production in the tissues, increased muscular tone, release of adrenaline and possibly of thyroxine. Tissue metabolism increases, with a resultant increase of heat production. If the environment be too warm, equivalent heat production is not needed and tissue activity and muscular tone diminish. It is probable that the general lethargy of the individual encountered on a hot day may be due to the decreased tone of his muscles because of the diminished heat production.

(2) Heat Elimination: Heat is eliminated from the body as a result of physical processes. It is lost in the warmed excretions, in vaporizing the water exhaled in expiration and from the skin surface by radiation and convection. The amount lost from the skin depends upon two factors, (a) the temperature of the body surface, which in turn depends upon the internal temperature. If the internal temperature is excessive, as in exercise, there is necessity for increased heat dissipation and the skin becomes warmer by cutaneous arteriolar dilatation, (b) the temperature gradient between the body surface and the environment. If

*An abridgement of a paper read before the University of Western Ontario Physiological Society, Dec. 5, 1939.
this be great, much heat may be readily lost from the surface, thus determining the degree of cutaneous vasodilatation. If the gradient is steep, the necessity for vasodilatation is not so prominent and the skin may not be flushed. If, as occurs on a hot day, the temperature gradient is lessened, more extensive superficial vasodilatation will occur in an attempt to dissipate the equivalent amount of heat. If caloric exchange between the body and the environment is hampered by a very low gradient as in hot weather, or if the exchange is not rapid enough due to excessive heat production, a new mechanism is called into play—the sweating mechanism. Water is poured out of the sweat glands, evaporates and absorbs heat in the process. The evaporation of sweat from the skin surface depends upon the humidity of the atmosphere. If this is low, evaporation occurs easily, but if the air is humid, evaporation is impeded and this cooling mechanism is lessened even although the sweat may still pour out of the body. This would explain the discomfort occasioned by a hot, humid environment.

The physical regulation of the body temperature refers to the processes involved in increasing or diminishing heat loss. It is a water-shifting mechanism whereby warm blood is shifted to the periphery by cutaneous vasodilatation so that heat may be dissipated by the physical means of radiation, convection and sweating. In this manner heat loss is increased. Exposure to cold causes cutaneous vasoconstriction, thus shifting the peripheral blood to the warmer interior so that heat loss is diminished.

Temperature Control: Chemical regulation and physical regulation work together in maintaining a constant body temperature. Any interference with either may cause an elevation or depression of the body temperature. With the body temperature so remarkably constant, the need is seen of a central co-ordinating centre which regulates these opposing processes. The role of the autonomic nervous system in tissue metabolism and, therefore, in heat production, has been known for a long time. Whether the sympathetic system plays an active part in heat production is a matter of debate among physiologists. We do know, however, that the sympathetic system tends to promote expenditure of energy (catabolism) and that the parasympathetic system tends to build up and conserve energy (anabolism). Alpern believes that the sympathetic nervous system plays an active role in heat production. That it most certainly plays a passive role by virtue of its heat conservation ability (peripheral vasoconstriction) has been clearly shown by Canon and his associates and more recently by Sawyer and Schlossberg.

Recent evidence indicates that the vegetative system is co-ordinated by higher autonomic control centres situated in the hypothalamus. There is also evidence that a heat production centre exists in the posterior hypothalamus (thought to be a sympathetic control centre)
TEMPERATURE REGULATION AND THE MECHANISM OF FEVER

and that the mechanism for heat loss is mediated through certain anterior hypothalamic nuclear groups, possibly parasympathetic in function. Clinical lesions of the posterior hypothalamus produce hypothermia because of their effect on the nuclear groups involved in heat production. Lesions in the anterior hypothalamus produce hyperthermia because they interfere with heat loss. It is probable that bacterial toxins may affect these centres and in such manner produce fever.

If the temperature centre concept is accepted then it is probable that the centre is constantly being affected by its blood supply and by nervous impulses and that the centre is constantly contacting the lower somatic and vegetative centres. We may thus liken the temperature centre to a thermostat which physiologically functions at one level of activity, regulating heat production and heat elimination, so that the body temperature is maintained fairly constant regardless of changing environmental conditions. We may also reason logically that the level of the thermostat is altered by pathological conditions, thus causing a change in body temperature.

Fever: It is popularly held that in fever the temperature-regulating centres have been set at a higher level of activity. This higher level of central activity is manifested by the higher body temperature. It is assumed that the balance which exists normally between heat production and heat elimination is temporarily altered in favour of heat gain and is then maintained at this higher level. Fever would, therefore, be a condition of positive heat balance. Evidence for this higher setting of the thermostatic level lies in the fact that the fevered body can still respond to temperature changes, but the response with the centre in a higher gear, will now depend upon this new fever level. When an individual with fever is exposed to cold, the cutaneous vessels constrict, muscular tone increases and shivering may occur. Exposure to heat or performance of exercise will cause cutaneous vasodilatation and sweating. Thus, the body in fever reacts to temperature changes but from a different thermostatic level, even although the response is not quite as efficient.

Assuming that in fever, the centre is set at a higher level, the question arises as to how the temperature rise is brought about. Morgan in a recent series of experiments with typhoid toxin reports that he found cytologic changes in an anterior and lateral hypothalamic nuclear group following the production of fever. This would indicate that certain bacterial toxins produce fever by a central action.

Physiologists are in accord that the initial change which occurs in the onset of the fever is a disturbance of the heat loss mechanism. This is well shown at the beginning of the disturbance when the skin is pale from the vasoconstriction and dry from the sweat inhibition. Even the blood flow through the periphery has been found to be diminished. Something disturbs the heat eliminating mechanism either through
central action or through peripheral action, causing it to “backfire”; heat is thus retained in the body and the temperature rises. As the body temperature rises, the metabolism increases due to the accelerating effect of heat on the chemical processes. Thus we see that the increased metabolism which occurs in a fever is mainly dependent upon the increase of the body temperature and not one of its causes.

Woodyatt and his associates suggested that the big factor in impairing the heat loss mechanism was a reduced blood volume due to the peripheral action of the toxins on the tissues. This toxic action increased the tissue osmotic pressure by increasing the hydration capacity of the cell colloids enabling them to bind the free water. The loss of fluid to the tissues resulted in a reduced circulating blood volume, especially at the expense of the peripheral or surface blood, with a resultant cooling of the skin. This cooling or relative cooling would then set up the nervous regulation against cold (i.e., peripheral vaso­constriction, increased heat production through the chill mechanism, etc.).

Barbour and his associates in their studies of experimental fevers showed that the liver takes up considerable amounts of fluid at the onset of a fever. This would indicate that water retention by the liver plays a leading role in hampering heat loss. The rationale of “pushing fluids” during fevers probably lies in the fact that this tends to combat the blood concentration which results with the reduced circulating blood volume.

As for the chill mechanism, there is still much to be learned. Certainly it produces a rapid temperature rise, but we have already seen that there is first a disturbed heat loss mechanism and then active heat production. “Chill” results from the invasion of the blood stream by the pyrogenic agent, but all fevers are not associated with chill. The chill may be due to an actual cooling of the skin or a relative coldness as compared to internal regions since the skin itself is hot in many cases. It is probable that the chill arises from the disturbance of heat loss, certainly it is secondary to it.

Cramer’s humoral theory of fever is suggestive. He presented evidence to show that certain bacterial toxins caused a release of the calorigenic, sympathetic stimulating hormones, adrenaline and thyroxine. Mimicking sympathetic action, these would diminish the heat loss by vasoconstriction and either primarily or secondarily increase the tissue heat production.

Morgan showed that clamping the blood supply to the thyroid when the temperature was elevated produced a rapid fall of the temperature. However, in most of the cases it did not fall back entirely to normal, which would indicate, he stated, “that the thyroid plays some role in fever but that there are also other factors involved.”
Pinkston demonstrated that release of adrenaline occurred in fever. Further evidence points to pyrogenic agents and bacterial vaccines as causing a secretion of adrenaline and thyroxine.

**Benefits of Fever:** There is much evidence that fever stimulates the reticulo-endothelial system and leucocytes to greater phagocytic activity. The viability of certain micro-organisms is impaired by the higher temperature and the rate of formation of immune bodies is greatly increased. These reactions are due to the increased temperature and subsequent increased metabolism of the body. It has also been shown that the formation of immune bodies does not take place until the temperature has risen. Thus the fever since it increases the metabolism of the cells increases the resistance of the body to infection. It would appear that the temperature rise is the essential factor in the defensive reaction of the body which we call fever.

**SUMMARY**

The body temperature is controlled by diencephalic centres which act like a thermostat and co-ordinate the chemical and the physical regulation of the processes involved. The onset of fever is caused by a disturbed heat loss mechanism. This might occur conceivably through a central action on the hypothalamic thermostat, diminishing heat loss and causing peripheral vasoconstriction, or through a peripheral action on the tissues causing reduced blood volume with haemoconcentration. This hampers heat loss, since the heat-conducting function of the blood is lessened by the diminished circulating blood volume. Reduced blood volume also reflexly causes peripheral vasoconstriction with a resultant feeling of chilliness and subsequent production of a body response to the cold. The thyroid and adrenal glands may play an important role in the disturbed heat loss mechanism through their calorigenic function. The "raison d'etre" of some forms of fever is that they are defensive reactions of the body.

The author wishes to thank John Lindsay, Meds. '43, for his aid in the preparation of this paper for publication.

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ACUTE APPENDICITIS: A TWENTY-YEAR CLINICAL SURVEY
By LOUIS J. MORSE and MILTON J. RADER
Ann. Surg. 3:2, 1940

"Acute appendicitis still remains a mocking challenge to those who practice the art and science of medicine, in spite of all the advances made by surgery during the past two decades."

Prefacing their paper with this statement, the authors go on to present a very interesting survey of the mortality rate of appendicitis. They point out that the average hospital mortality rate today for the whole of the United States is a little over 10%—just what it was 20 years ago.

The authors present their analysis of nearly 9,000 cases operated upon at the Jewish Hospital, Brooklyn, over a 20-year period, with special reference to mortality rate, age incidence, and time element. The value of early operation is shown by the remarkably low mortality rate in early cases. When operated upon within 24 hours of onset of symptoms the mortality represents almost the irreducible minimum (0.6%). High mortality results when much peritoneal involvement occurs. Diffuse peritonitis (“a blot that must be eradicated”) carries a very high mortality rate (33%). The diagnostic value of temperature, pulse rate, and white blood count is discussed and the usefulness of the McBurney approach is stressed.

—J. G. STAPLETON.

THE USE OF ANTISEPTICS IN OPEN WOUNDS
By W. L. ESTES, JR.
Am. J. Surg., February, 1940

Efforts to treat an open wound to promote rapid healing without infection must be directed first to the control of hemorrhage, and then to the removal of all debris and devitalized tissues by irrigation with saline, but so gently, carefully and thoroughly as to wash out and rid the wound of every free necrotic bit, but not to damage the healthy tissue remaining. The most essential adjunct is debridement, or excision of all the devitalized and contaminated tissue that is not free and cannot be washed out.

Antiseptics are of value in skin disinfection, but in the treatment of the wound itself are seldom necessary, and their indiscriminate use may harm normal processes of repair. An antiseptic, however, would be an added safeguard in anaerobically or soil contaminated wounds. In this category, it is suggested that Dakin’s solution may be used. An ideal antiseptic for use in open wounds should possess effective bactericidal action and be non-toxic to tissues, and not interfere with or delay healing.

—R. H. CRAM, ’41.

THROMBOPHLEBITIS: THE ROLE OF VASOSPASM IN THE PRODUCTION OF CLINICAL MANIFESTATIONS
By OCHSNR and DEBAKEY
J.A.M.A., 114:2, 1940

The authors present the clinical and experimental evidence to prove that many of the symptoms and signs of thrombophlebitis are due to vasospasm of the arterial and venous systems, and that the vasoconstricting impulses originate in the thrombophlebitic segment. The results are increased filtration pressure, relative anoxia of the capillary endothelium, and diminution in the flow of lymph, all of which increase the amount of perivascular fluid. By interrupting the vasoconstrictor impulses with procaine infiltration of the sympathetic ganglia there is produced a re-establishment of the normal exchange of intravascular and perivascular fluids. This procedure was done in fifteen
patients with prompt and permanent relief of pain in all instances, subsidence of edema within twelve days, and a normal temperature in two to seven days. Although the performance of nerve block as recommended by the authors is not without danger, their results are impressive enough to warrant further investigation.

—J. A. Chikovsky, '41.

**SERUM PHOSPHATASE IN LYMPHATOID DISEASE**

*By H. Woodward and L. Craven*

*J. Clin. Inv., January, 1940*

Inasmuch as serum phosphatase values are allied in Paget's disease of the bone, rickets, and other bone diseases, the authors decided to review the changes in this enzyme which might occur in the lymphomata.

The authors are convinced that bone changes occur in the lymphomata much more commonly than is usually suspected. They claim that 50% of five-year cases show gross bone changes. Their work tends to show that serum phosphatase estimations will indicate bone involvement long before it is shown clinically or by X-ray. In the case of the Hodgkin's patient who is doing badly, yet who has little accessible adenopathy, a high serum phosphatase may be taken to indicate a bone lesion which later will become evident to X-ray with still higher serum phosphatase values. There does not seem to be any definite relationship to serum phosphatase changes in leukemia and lymphosarcoma.

—F. Sypher, '41.

**CURABILITY OF CARCINOMA OF THE RECTUM**

*By T. E. Jones*

*Surg. Gyn. & Ob., 70:2A, 1940*

In this article the author discusses the problem that confronts the surgeon after the diagnosis of rectal carcinoma has been made. He enumerates: (1) Location and fixation, (2) Obstruction, (3) Obesity, (4) Size of the growth, as the points which must be considered before deciding on operability of the growth.

His philosophy regarding cancer of the rectum is to increase the scope of operability constantly. He points out that the operative mortality may be increased a little, but that a relatively greater number of patients will be alive at the end of five years than with a lower percentage of operability.

—D. Keeley, '41.

**THE MANAGEMENT OF CHRONIC PELVIC INFECTIONS**

*By George H. Gardner*

*Surg., Gyn. & Ob., 70:2A, 1940*

The author states that although pelvic infections still occupy an extremely important position among gynecological problems, tubal disease is a less frequent indication for surgery nowadays. He feels that cul-de-sac drainage via posterior colpotomy is instituted too frequently, and that it should be reserved for a bulging pelvic abscess, when there is a persistent fever, a high leucocyte count, and when clinical observation has demonstrated that the patient's general condition is not improving. He recommends drains through the posterior vaginal fornix, rather than through the abdominal wall. He says that only about 20% of women who have suffered from pelvic infections require surgical interference. The etiology of violin-string adhesions over the liver is discussed and they are related to genital gonorrhea. In conclusion, he recommends that if one ovary is diseased and the other one normal, the diseased ovary should be removed in toto and the subsequent surgical menopause treated by endocrine therapy.

—D. Keeley, '41.

**REMOTE EFFECTS OF TOXEMIA OF PREGNANCY**

*By Milton S. Lewis*

*Southern Med. Jour., 33:1, 1940*

This paper deals with the results of 12½ years' enquiry into the remote effects of toxemia of pregnancy. Primarily it is concerned with the significance of recurrent toxemia and the development of permanent vascular renal damage. 107 cases with another pregnancy subsequent to an attack of toxemia are dealt with. Of these cases, 70 were of convulsive and 37 of non-convulsive toxemia.
Of the non-convulsive patients 61.4% developed recurrent toxemia, 25.7% had no ill effects following the toxemia, and 12.8% developed permanent renal damage. Of the convulsive patients 48.6% developed recurrent toxemia, 40.5% had no ill effects, and 10.8% developed permanent vascular renal disease. In the development of the permanent vascular renal disease the duration and severity of the toxemia before birth of the child seems to be important. The age, parity, and degree of hypertension may also be significant.

Recurrent toxemia may occur in the absence of any detectable signs of renal damage. Therefore, long-continued observation of the post-toxemic patient will improve the prognosis both for future pregnancies and for life.


RESULTS OF AMBULANT TREATMENT OF PEPTIC ULCER

By David Ferriman
B.M.J., February 10, 1940

This paper reports the results of ambulant treatment of 42 cases of uncomplicated chronic gastric or duodenal ulcers. They were not given the usual hospital treatment largely for economic reasons.

The patients were allowed to go to work as usual. They were forbidden red meat, spices, spicy foods and alcohol, and were permitted a maximum of 10 cigarettes a day. Six meals a day were rigorously enjoined. Alkalis, sedatives, and anti-spasmodics were also used. Radiographs were taken every three months and treatment was continued for some months after radiological “healing” (disappearance of crater and all signs of local tenderness and spasm).

The proportion of cures is high (about 75%) and it is concluded that valuable results may be expected from the operation of peptic ulcer clinics.

—J. G. Stapleton, ’41.

TRANSFUSION OF CITRATED BLOOD IN ARGENTINA

Informaciones Argentinas, 37:27, 1939

It is not generally known that twenty-five years ago, on November 9th, 1914, Dr. Luis Agote, now Professor Emeritus of the Faculty of Medical Sciences, Argentina, applied for the first time the method of transfusion of citrated blood, an event of singular importance in the field of scientific achievement of the present century.

The addition of sodium citrate to blood before transfusion gave to the procedure advantages which it had formerly lacked, and it has remained a widespread practice despite the multiple and varied procedures since suggested.

In November 1939 a tablet commemorating the first transfusion of citrated blood as suggested by Agote was unveiled in the Rawson Hospital in Buenos Aires.

—Translated by F. F. Bennett, ’43.

USE OF MALE SEX HORMONES IN TREATMENT

By P. M. F. Bishop
The Practitioner, February, 1940.

The preparations available for clinical use are testosterone and androsterone. Testosterone is about six times as active as androsterone; the form usually used is testosterone propionate (the esterification of the hormone prolongs its period of activity so that injections can be restricted to about twice a week). The only practical mode of administration at the present time is by intramuscular injection, although percutaneous administration in the form of an ointment has been tried experimentally, with results quite inferior to those of intramuscular injection.

In the male the hormone is of definite value in castrates, eunuchoidism, premature senility. It is also of value in delayed sexual development, cryptorchidism, defective spermatogenesis and male sterility, although in these conditions gonadotropic therapy is more logical.

There is considerable evidence to show that the hormone can arrest the changes produced in the prostate by estrogens, i.e., enlarged prostate. However, its value is not yet sufficiently established to warrant endocrine therapy replacing operation.

In the female its main use is in menorrhagia, where it produces temporary atrophy of the endometrium, inducing a phase of amenorrhea which, it is hoped, may be succeeded by resumption of the normal menstrual rhythm.

—D. H. Woodhouse, ’41.
C. A. M. S. I.

"The aims of this organization shall be to further the welfare and interests of Canadian medical students and internes, to promote co-operation between medical students, and between internes and hospital staffs, and to provide a medium for co-operation and interchange of ideas between the medical schools and hospitals of Canada, and with kindred organizations."

The above statement is of the official aims of the Canadian Association of Medical Students and Internes. This organization is a very recent arrival in the life of the Canadian medical school. It was conceived in the minds of a small group of medical students at the University of Toronto and the first annual convention was held in Toronto, March 13th, 1938. Since then, communication has been established with all of the nine Canadian medical schools and, at the recent conference in Kingston, eight of the schools were represented. Western has been interested in C. A. M. S. I. since its inception and delegates, appointed by the Hippocratic Council, have represented our school at each meeting.

For such a young organization, the achievements and activities of C. A. M. S. I. are many and varied. Contacts have been established with the Canadian Medical Association and the Association of American Hospitals. The Interne Board, which seeks to establish a satisfactory system of Junior Interne appointments, functioned to a degree last fall and is a result of C. A. M. S. I. organization. The Interne Board will be of growing importance for future graduating classes. Comprehensive studies are being made of tuberculosis in medical students, student health, co-operatives, curriculum, interne maintenance and education.

The time has now arrived for us at Western to establish a local chapter for the purpose of leading the various C. A. M. S. I. activities here. Western medical students should be acquainted with this important development in Canadian medical student life.

—RAY Stubbing.
Books in Review

THE PHYSIOLOGICAL BASIS OF MEDICAL PRACTICE

By C. H. Best

Professor and Head of Depart. of Physiology, University of Toronto
and N. B. Taylor

Professor of Physiology, University of Toronto.

(Second Edition, 1872 pp., Illustrated, Indexed, $10.00. Williams & Wilkins, Baltimore, 1939)

One of Osler’s most famous aphorisms was to the effect that “As is our Pathology, so is our Practice.” But, without discounting the worth of pathology, many modern clinicians would substitute the science of physiology in this dictum. Completely brought up to date, Best and Taylor’s “Physiological Basis” is now in its second edition.

As a link between the laboratory and the clinic, this book is of inestimable value both to the student and the practitioner. In many of the continent’s most outstanding schools it has completely replaced all other physiology texts and the numerous reprints of the first edition attest to its popularity. The book is of special value to those contemplating the higher degrees.

Aside from its incorporation of all the recent advances, the book’s general value has been enhanced by the addition of a new section of more than 250 pages dealing with the special senses.

One criticism might be timidly offered. It would seem to the reviewer that the sections dealing with the physics of light and sound are rather too detailed. But this does not in the least detract from the value of the book and it would be well if “Best & Taylor” were placed alongside “Gray,” as the great preclinical classics.

—A. S. DOUGLAS, ’42.

THE PSYCHOLOGY OF HUMAN CONFLICT

By Edwin R. Guthrie

(First Edition, 408 pp., $2.75. Harper & Brothers, 1938)

In the preface to this book concerning the clash of motives within the individual the author states his attempt at “a simplified description of the ways in which men adjust themselves to circumstances.”
BOOK REVIEWS

The work is comprehensive of its subject in its elements and can be read and understood without any prerequisite knowledge of any system of psychiatry or psychology. It deals, not so much with the definitely psychotic individual, but with the butcher, the baker and your ulcer patient. It provides a rationale of why and how mental knots arise.

Very readable, it is a ready aid to human understanding.

—WARD REASON, '42.

SURGERY OF THE HAND

By JOHN HAROLD COUCH, M.A., M.B., F.R.C.S. (Edin.)
Dept. of Surg., University of Toronto, and Toronto General Hospital.

(Foreword by W. E. Gallie. Illustrated. $1.50, 1939. University of Toronto Press)

This is one of the smaller books which every medical student and practitioner should add to his library, for in it are the essentials of good treatment of all the common hand injuries and infections which one sees maltreated so often.

The author, relying upon ten years of intensive study and experience in this special surgical field, puts forth in a very clear and concise manner the treatment which he has found to give the best results. He deals with each of the infections and injuries separately and at the beginning of each chapter gives his plan of treatment.

The chapter on "Levels of Amputations" is of special importance and worth consideration. His principles of amputation being:

(a) Save function rather than form.
(b) Go back to healthy tissue rather than the old blanket rule "save all you can."

The many self-explanatory diagrams, together with the commonsense rationale and practical pointers, mark the book as one of the outstanding works in this field.

—DOUG. KEELEY, '41.
RECENT ACCESSIONS TO THE MEDICAL SCHOOL LIBRARY

Cushing—Consecratio Medici. 1940.
Cushing—The Medical Career. 1940.
Elvehjem and Wilson—Respiratory Enzymes. 1939.
American Association for the Advancement of Science—Mental Health. 1939.
Billings—Handbook of Elementary Psychobiology and Psychiatry. 1939.
Cole and Cole—Pneumoconiosis; the Story of Dusty Lungs. 1940.
Guilford—General Psychology. 1939.
Taussig—Abortion. 1936.
Simons—Primary Carcinoma of the Lung. 1937.
Strecker—Beyond the Clinical Frontiers. 1940.
Dickson and Diveley—Functional Disorders of the Foot. 1940.
Katz—Electric Excitation of Nerve. 1939.
Dictionary of National Biography from the Beginning to 1930. 1939.
Wechsler—The Measurement of Adult Intelligence. 1939.
Canadian Medical Association; Committee on Nutrition—Nutrition in Everyday Practice. 1939.