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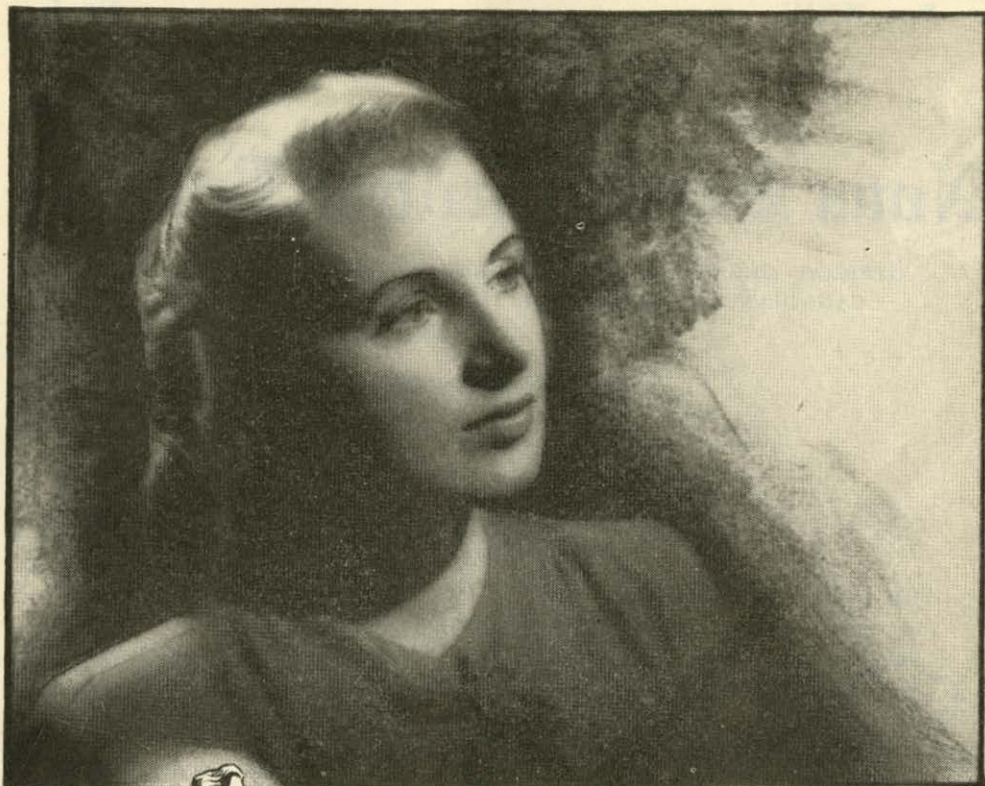
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# Methyl Alcohol Poisoning\*

## A Survey of Thirty Cases

D. J. TONNING M.D.

Saint John, N. B.

Mr. Chairman—Ladies—and—Gentlemen:

It is a great honour to me being invited to present a paper at the Dalhousie Refresher Course. I probably owe more to Dalhousie University than any other graduate, because not only did I receive my medical education here, but also was taught the English language.

### *Acute Methyl Alcohol Poisoning:*

In June of this year 90 persons suspected of having consumed methyl alcohol were brought to the Out Patient Department of the Saint John General Hospital, within a period of 48 hours. Thirty of these cases were admitted to the Medical Service. Eleven of these arrived in a comatosed state with marked cyanosis and convulsions.

These eleven cases died—their period of hospitalization varying from 4 minutes to 12 hours.

I might add, that to make our dilemma complete, two cases of diabetic coma and one case of uremia due to acute glomerular nephritis were admitted for diagnosis at the same time.

Instead of quoting each case separately the following were the average findings:

### *A. History:*

From 24 to 72 hours previous to admission these persons had consumed "Methanol" the quantity varying from 6 oz. to 1½ pints.

The Methanol seized by the authorities contained 97-99% methyl alcohol, estimated by the specific gravity and the refractive index.

Immediately no ill effects were noted except symptoms of intoxication similar to ethyl alcohol. Then, there followed a period of 6 to 72 hours which were absolutely symptom free.

### *B. Symptoms:*

Their main symptoms, prior to becoming unconscious, were of sudden onset with severe crampy abdominal pain, blurred vision, and pain in the eye-balls, severe shortness of breath with a feeling of uneasiness, marked perspiration and a severe thirst.

### *C. Physical Findings:*

(1) Skin: Cold, clammy with profuse perspiration. There was a marked pallor over-shadowed by cyanosis. This was a constant, and we felt, a diagnostic feature of the condition.

(2) Eyes: Slight protrusion. Pupils were dilated with variable reaction to light and accommodation, and often absent in severe cases. Eye-balls were tender to pressure and in a few cases ptosis of the lids was found. Retina showed some hyperaemia and minor degree of oedema of the optic disc.

\* Paper presented at the Dalhousie Refresher Course, Halifax, October 13, 1944.

Cardio-Vascular System. Pulse: Rate 78-120 per minute, regular in time and volume. B. P. 90/60 to 160/90.

(3) Respiratory System: Marked irregularity in movements, often spasmodic and as if the patients were in agony. Rate varied from 4 to 30 per minute. Examination of chest was negative.

(4) Central Nervous System: No constant findings, and the cases varied from irritability to unconsciousness. In some, reflexes were hyperactive, in others completely absent.

*D. A provisional diagnosis of acute methyl alcohol poisoning was made.*

### LABORATORY FINDINGS

#### (1) Urinalysis.

Negative, except for the following: never more than 20 mgs. of albumin and formic acid in excess amounts.

#### (2) Blood Picture.

Hb. 85% to 117%.	Average: 98%.
R. B. C. 4,190,000 to 5,500,000.	Av. rage: 4,685,000.
W. B. C. 5,500 to 33,700.	Average: 11,350.
Differential showed slight increase in neutrophils, otherwise negative.	
Clotting time: 3 to 6.5 minutes.	Average: 4.12 minutes
Bleeding time: 1 to 5 minutes.	Average: 2.33 minutes
Red Cell volume: 51 to 61%.	Average: 57%

#### (3) Blood Chemistry.

Total Proteins: (serum). 4.3% to 5.5%.	Average: 4.77%
Albumin: 4.1% to 4.2%.	Average: 4.15%
Chlorides: 467 mgs./100 cc. to 470 mgs./100 cc.	Average: 468.5 mgs./100 cc.
Cholesterol: 145 to 223 mg./100 cc.	Average: 174.2 mgs./100 cc.
Lactic Acid: 74.3 mgs./100 cc.	Average: 74.3 mgs./100 cc.
Methyl Alcohol: (Admission) 0.017 to 0.375%.	Average: 0.098%
CO <sub>2</sub> combining power: 13 to 64 Vol. %.	Average: 49.9 Vol. %
Icteric Index: 7.5 to 15 Units.	Average: 9.8 units
Van Den Bergh: Direct 0.22 mgs./100 cc. (in all cases).	Average: 0.22 mg./100 cc.
Indirect: 0.27 to 0.44 mg./100 cc.	Average: 0.36 mg./100 cc.
N. P. N.: 34 to 48 mg./100 cc.	Average: 40.6 mg./100 cc.
Uric Acid: 1.7 to 5.4 mg./100 cc.	Average: 3.11 mg./100 cc.
Urea Nitrogen: 10.5 to 18.5 mg./100 cc.	Average: 13.3 mg./100 cc.
Creatine: 1 to 1.8 mg./100 cc.	Average: 1.30 mg./100 cc.
Stomach contents: Varied from weakly to markedly positive for methyl alcohol for as long as 3 days after drinking.	
Spinal Punctures: 50% of the cases.	
Normal Pressure: Average 115 mm. of water.	
Fluid clear: Pressure applied to Jugular 220 mm. Cell count: 3-5.	
E.K.G.: Normal.	

It is of importance to note that in 2 cases where respiration had ceased but heart action still persisted, were kept alive for 2 hours in the iron lung. Wasserman and Kahn Tests: Negative in all cases, but two, who were known to be syphilitic.

## FINDINGS AT AUTOPSY

## GROSS

Appearance	Brain	Stomach	Heart's Blood
E. Indian	Oedema	Congested	Unclotted
Cyanotic	"	"	"
"	"	"	"
"	"	"	"
"	"	"	Some Clot

## TEST FOR METHANOL

Case	Stomach Qualitative	Blood
Case 1.....	Positive	0.297%
" 2.....	"	0.239%
" 3.....	"	0.10 %
" 4.....	"	0.19 %
" 5.....	"	0.21 %

*Microscopic:*

**Eye.**—Little change in the optic nerve. The ganglion cells of the retina show irregular staining, eccentric nuclei, fraying, vacuolation and autolysis. No lesions in the gliae cells.

**Brain.**—Different degrees of oedema and hyperaemia with occasional punctate haemorrhages, and accumulation of brown pigment in the neurons.

**Lungs.**—Engorgement of vessels.

**Liver.**—Parenchymatous degeneration.

**Kidneys.**—Essentially negative.

**Stomach.**—Superficial necrosis and mucous distensions of epithelial cells. Some wandering cells.

**Analysis:** of 11 samples of the seized "liquor."

8 samples contained 97%-99% methyl alcohol.

3 samples contained 32%-51%-91%.

*E. Final Diagnosis:*

Acute methyl alcohol poisoning.

*F. Treatment:* This comes under two headings:*Preventive:*

This was done by the seizing of all contraband liquors by the police and a prompt warning over the radio, press and public speaking facilities that methyl alcohol had been consumed by many people with disastrous effects, and so on.

*Curative:*

In treating these individuals we were guided by the following:

(1) A definite history of having consumed methyl alcohol.

(2) Symptoms, signs and physical findings suggesting acidosis.

- (3) Laboratory findings showing:—Methyl alcohol in the stomach and blood, formic acid in the urine, low  $\text{Co}_2$  combining power and increased lactic acid concentration in the blood.
- (4) Pathological findings of cellular oedema of the brain and destructive process in the retina.

The fate of methyl alcohol in the human body is not definitely known. As a working hypothesis one can consider that it is a poisonous compound which by its slow and incomplete oxidation forms two intermediate products in the body—namely formaldehyde and formic acid. It has been suggested in the literature that all three of these substances may have direct toxic action on highly specialized tissues, such as the brain and retina of the eye. Also formic acid is said to interfere with the normal production of the respiratory enzyme, and thus may lead to respiratory failure. This, in turn would increase the lactic acid concentration of the blood and result in an acidosis. The latter again, leads to poor cellular oxidation and an increase in the lactic acid concentration in the tissues themselves. In the case of the retina, whose cells are very sensitive to poor oxidation, such a high concentration of lactic acid may be produced as to cause a degeneration of the nerve-end plates.

Therefore, the main points in the treatment were:

1. To combat the acidosis as quickly as possible.
2. To reduce the cellular oedema of the central nervous system.
3. To assist in the elimination of the methyl alcohol and its deleterious by-products.

#### *Acidosis:*

Acidosis or often spoken of as alkali deficit is due to loss of alkali or retention of acids. Loss of alkali is most common in diarrhoea, continuous vomiting and gastric lavage. (In severe cases the opposite, i.e. alkalosis may result.)

Retention of acids, which includes production of organic acids faster than they can be excreted is common in diabetes, nephritis, anurea following sulphonamide therapy or blood transfusions and in starvation, dehydration and in practically all moribund states. Therefore it is important to know which type of acidosis one is dealing with, the degree of acidosis and any underlying cause.

In general, the way of prophylactic treatment should be an attempt at prevention by recognition of the causes of acidosis,—such as prompt control of diarrhoea, and vomiting, free administration of fluids in illnesses, careful regulation of diabetes, attempts at elimination and diuresis in nephritis, proper blood grouping and keeping urine alkaline in reaction in transfusions, proper blood concentrations of sulphonamides with continuous measurements of fluid intake and output and so on.

When acidosis is established, its treatment often differs with the cause. As for example: removal of sulpha crystals from the kidney by cystoscopic means:—diabetic acidosis by giving fluids, carbohydrates and insulin.

Very often it is necessary to inject an alkali intravenously as an emergency. Different types of alkali mixtures have been used. They are:

- (1) (1.3%) Sodium bicarbonate.

I have always felt that by using sodium bicarbonate, we have a rapid change of the  $\text{Co}_2$  combining power, and may very readily produce an alkalosis.

This sudden change may be deleterious and should oedema be present, an irreversible condition may be set up which may be fatal.

(2) Potassium citrate 5%.

Potassium citrate is not used very often. I have used it in anuria following transfusions, (i.e.) (Formation of acid haemoglobin with crystallization in the tubulus of kidney in an acid urine) with very good results. The change of  $\text{CO}_2$  combining power is not as rapid as by using sodium bicarbonate.

(3) One-sixth molar sodium lactate solution.

This is easily heat-sterilized without decomposition and forms a stable neutral and non-irritant solution. The term one-sixth represents a solution which contains one-sixth of a mol of sodium lactate in each 1000 cc. (one mol—122 grams— $1/6$  mol—18.7 grams).

Sodium lactate is more precisely referred to as sodium dextro and levo rotary lactate. This mixture contains equal parts of sodium d lactate and sodium l lactate. The d and l forms are optically active.

In solution containing equal concentrations the relations are equal in amount but opposite in direction. Therefore, such solutions are optically inactive but have physiological properties which are of practical importance, namely:—

The "d" lactic acid (sarcolactic acid) is a normal constituent of the blood and is stored in the liver as glycogen.

The "l" lactic acid is not a normal constituent of the body but is oxidized to sodium bicarbonate, and/or excreted into the urine.

Hence, this solution when injected into the blood stream,  $1/2$  is converted into liver glycogen while the other  $1/2$  appears to be oxidized to sodium bicarbonate. Therefore, it has an anti-ketogenic effect of glycogen and an acid neutralizing effect of bicarbonate at the same time. It gives rapid relief of acidosis, but its oxidation to sodium bicarbonate is gradual enough to prevent serious alkalosis, even if a somewhat excessive amount is administered.

*Ringers Lactate Solution:*

As it was necessary to force fluids in these patients, they were given 500 to 1000 cc. or more of the Ringers lactate solution according to the clinical picture and the  $\text{CO}_2$  combining power.

Repeated infusion of sodium chloride alone may result in a fall of plasma bicarbonate, potassium and calcium. The loss of bicarbonate is particularly undesirable because it exacerbates the acidosis which already existed.

It was felt that the plasma used in these cases,—as will be discussed later—also acted as a buffer.

The Ringers lactate solution contains per 100 cc.:—

0.31 grams Sodium d—l lactate.

0.6 " Sodium chloride.

0.03 " Potassium chloride.

0.02 " Calcium chloride.

During the infusion the following changes were noted in the patients:

- (1) The respiration returned to normal and the cyanosis faded.
- (2) The perspiration ceased and the color of skin returned to normal.
- (3) The severe crampy abdominal pains disappeared.

- (4) The pain in the eye-balls lessened and some improvement of the blurred vision occurred.
- (5) The patients had a feeling of well-being, comfort and relief from the agony they had gone through.

2. To relieve the cellular oedema of the central nervous system.

In order to lessen the oedema, as well as being a diuretic, 50 cc. of 50% glucose was given intravenously immediately. This was followed by 125 cc. of double strength plasma—the plasma being given very slowly.

3. To assist in elimination of the formic acid.

It was clearly demonstrated that there were no physical or laboratory findings of serious myocardial, liver and kidney damage, or pulmonary oedema.

In addition, and in spite of the pathological findings of cellular oedema of the brain, all the spinal fluid pressure readings were found to be normal. Therefore, force fluids of 5% glucose in sterile water was given intravenously without hesitation. The amount varied from 1000 to 3000 cc. per 24 hours pending on the amount taken by mouth. At regular intervals the haematocrit, the plasma protein and chlorides were estimated.

In addition our routine treatment included:

- (1) Absolute bed-rest.
- (2) Free administration of oxygen.
- (3) Gastric lavage, where possible, using sodium bicarbonate.
- (4) 20 mg. of thiamin chloride and caffeine sodium benzoate intramuscularly q.4h.
- (5) Protection of the eyes from light.
- (6) Potassium citrate by mouth.
- (7) Some cases also received ethyl alcohol by mouth.

This practice was discontinued because it appeared that the ethyl alcohol was poorly oxidized, as daily blood estimations of ethyl alcohol concentration became alarmingly high.

With this method of treatment the acidosis was overcome within a very short time—clinically within 15 to 20 minutes, and from a laboratory point of view, within 2 to 24 hours.

In general the recovery was uneventful with no residual pathology demonstrated except marked eye changes in 1 case at the time of discharge from the hospital.

After a period of 3 1/2 months, an eye follow-up was obtained in five cases. In all but one case the vision was normal. The nerve heads were all uniformly hyperaemic. The peripheral fields were full.

In one case with normal vision the light reflex was sluggish.

One man presented normal vision in the right, but in the left eye the vision was 20/300. This man's vision deteriorated early in his illness and never was restored. The light reflex in the left eye is sluggish, but a consensual reflex is present.

The peripheral field was full. The nerve head showed a definite atrophy.

It is felt that the cases showing some hyperaemia should be followed as it is possible atrophy may develop even in a period of months.



*Conclusion:*

1. A series of 30 cases of acute methyl alcohol poisoning has been discussed.
2. The cases included all ages from 16 to 60 years.
3. Eleven cases died, most of these being habitual drinkers.
4. Nineteen cases survived, with a small percentage of eye lesion.
5. The  $\text{CO}_2$  combining power often was normal at admission but in a few hours would be very low and patient in a critical condition.
6. Lactic acid in the blood and formic acid in the urine were found to be much higher than normal.
7. We were really dealing with a retention acidosis rather than a true respiratory type of acidosis.
8. We found the use of Ringer lactate solution, 50% glucose, double strength plasma, 5% glucose in sterile water and vit. B. the most successful type of treatment. It may be stated that after this routine treatment had been instituted, we had no further deaths, and also that this treatment could be carried out satisfactorily, without elaborate laboratory facilities.
9. That methyl alcohol was found in the stomach as long as three days after consuming it, may lead one to believe that methyl alcohol may be excreted through the stomach and that a continuous gastric lavage should be done.
10. Furthermore methyl alcohol was present in the blood stream from 7 to 14 days after admission to the hospital.
11. Due to the confusion of so many acutely ill persons being brought to the hospital in such a short time, we were unable to give each case as much attention and investigation as we would have liked to.
12. That acute methyl alcohol poisoning is primarily a medical emergency.

This work was done in the closest co-operation with the various departments of the hospital.

I wish to thank, specifically, the following: Dr. Arnold Branch, Mr. Robert Washburn, and Miss Miron McGeouch, of the Laboratory; Dr. R. T. Hayes, of the Department of Ophthalmology; Dr. Graham Knoll, of the Department of Medicine; Lt.-Col. W. O. McDonald, Major G. C. Gaulton, and Capt. O. Herscovitch, of Military District No. 7, Saint John; and Flt.-Lt. J. A. MacDougall, of the Royal Canadian Air Force, Dartmouth.

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# Carcinoma of the Ampulla of Vater and of the Head of the Pancreas\*

G. F. SKINNER, M D., F.R.C.S.(C.)

Saint John, N. B.

CARCINOMA of the ampulla of Vater and carcinoma of the head of the pancreas involve three important organs at a very early stage, namely, the duodenum, the pancreas and the biliary ducts. Consequently, to define our subject a few words about the tumor pathology of these three regions might not be out of place. Benign and malignant tumors of the duodenum are very uncommon, except in this one location, as is well illustrated by the fact that we so completely disregard the cancer problem in our treatment of duodenal ulcers.

Tumors of the pancreas occur more frequently, but until recently pathology of this inaccessible organ was usually considered beyond the reach of surgery except for the doubtful surgical assistance in acute pancreatitis, and the occasional more or less elective removal of a benign cyst. But if our immediate predecessors could consider most lesions of the pancreas beyond their responsibility, this no longer applies to the present day abdominal surgeon. Improved anaesthesia, adequate treatment of shock, advances in endocrinology, and Vitamin K therapy have brought within the realm of practical surgery two distinct groups of tumors found in the region of the pancreas. We will not discuss at present the first of these two groups of neoplasms, adenomas and carcinomas of the islands of Langerhan occurring usually in the body and tail of the pancreas, and showing their presence by hyperinsulinism.

The following case illustrates the other group, those that manifest themselves by obstruction of the pancreatic ducts and the common bile duct—carcinoma of the head of the pancreas and so-called carcinoma of the ampulla of Vater.

Jaundice appearing without severe pain in a patient in the carcinoma age and persisting for more than a couple of weeks, must raise the possibility of such a tumor; and if this symptom is accompanied by a palpable gall bladder, which phenomenon every medical student knows as Courvoisier's law, the diagnosis is almost complete, or at least as complete as is possible without exploration, regardless of the number of bile and liver function tests that may be undertaken. But unfortunately the jaundice due to these lesions does not always remain painless nor is the gall bladder always palpable.

These malignancies of the papilla or ampulla of Vater were first described over a hundred years ago; and for many years they, along with most carcinoma arising from the head of the pancreas, have been known to produce this obvious alarm signal of jaundice, while still small and relatively well localized lesions. This fact at times has given this whole group of tumors the reputation of slow growth, of low-grade malignancy.

The truth is an early obstruction of the ducts rather than a benign character. This apparent slow clinical progress of the disease and the relatively benign microscopic picture seen in biopsies removed too superficially have

caused some to suggest that a considerable number are papillomas. This unfortunately is not true.

These malignancies vary in origin. They may start from the lining cells of the ducts, from the ampulla, from the papillary projection into the duodenum, from aberrant pancreatic tissue or from the nearby head of the pancreas, but the important common factor is that they present themselves as cases of obstructive jaundice.

Although very few of the patients seek treatment before the jaundice appears, yet after they present themselves, a story can be elicited of loss of appetite and loss of weight and strength existing for some weeks prior to the jaundice.

Occasionally diarrhoea may appear before the jaundice if the pancreatic duct is blocked first; or vice versa, jaundice may be marked with no interference with the flow of pancreatic juices (that is, normal pancreatic secretion may be obtained by duodenal intubation, with bile absent). Probably this latter finding is seen in cases in which the two ducts enter separately into the duodenum.

Anaemia is often an early symptom, due both to hemorrhage from ulceration in the cancer and to interference with the appetite and digestion.

No successful radical resection en bloc of malignant growths of the ampulla and head of the pancreas had been reported prior to 1935 for the following reasons:

- (1) The proximity of important structures made these lesions so inaccessible that the shock of a block dissection was prohibitive.
- (2) The hemorrhagic tendency of jaundiced patients had not been controlled until the recent introduction of Vitamin K.
- (3) Catgut sutures were quickly dissolved by any leak of pancreatic secretion.
- (4) Re-establishing the flow of pancreatic secretions into the bowel was always a most difficult technical problem.

This last fact was the most important for the duodenal secretions including secretin, and the pancreatic enzymes had been considered essential to life and health. All of these considerations caused surgeons to choose one of two procedures, either one of which was inadequate. In most cases only a short circuit operation had been done, between the gall bladder and stomach, duodenum or jejunum, to re-establish the flow of bile into the intestines. Because jaundice appeared so early in the disease, this procedure alone gave relief in some patients for a considerable period.

But even this simple operation produced a high immediate mortality rate, on account of the hemorrhagic tendency, and a high morbidity rate due to ascending cholangitis which frequently followed, especially if the gall bladder was anastomosed to the stomach. This last complication was overcome when the gall bladder was anastomosed to the jejunum instead of to the stomach.

Beginning with Halstead's case in 1898 a few local resections of the tumor had been undertaken through the transduodenal approach.<sup>1</sup> In this local resection the continuity of both the common duct and the pancreatic duct with the duodenum was re-established. This was a difficult technical procedure in spite of the limited area removed, but this operation gained favor for a time because of the mistaken belief in the relatively benign characteristics of the

tumor. However as follow-up statistics became available, recurrences after this very limited resection were seen to approach 100%.

In 1935 following a fatal outcome in such a local resection due to a duodenal fistula and peritonitis, A. O. Whipple<sup>2</sup> decided to undertake a much more radical resection in two stages. The first stage was to re-establish the bile flow and the second to remove the whole of the duodenum with the encircled portion of the pancreas. Whipple was influenced in this decision by the experimental work of Dragstedt<sup>3</sup> who in animals had demonstrated the following phenomena.

- (1) Dogs lived after complete removal of the duodenum.
- (2) After complete removal of the pancreas, dogs could be kept alive by the administration of insulin alone, but they developed gross fat infiltration of the liver. This latter condition could be prevented by feeding pancreas by mouth. Dragstedt concluded the benefit of this oral administration to be due to some other substance than pancreatic enzymes. He called this substance, lipocaic.
- (3) If part of the pancreas was left intact, but all the ducts were severed then the fatty infiltration of the liver did not occur. Consequently he concluded lipocaic to be a second internal secretion from the pancreas.

Since 1935 a considerable number of successful radical resections have been reported following the principles of Whipple's operation with only minor technical variations. The case here reported was operated nearly a year ago, and now for several months he has been working at his previous occupation as a baker.

### Case Report

A white male, age 41, was admitted to the medical service of the General Hospital in November, 1943, complaining of jaundice with cutaneous pruritis, weakness, loss of appetite, fever and a loss of 50 pounds.

In June of the same year he had noticed a loss of appetite and weakness which was followed a month later by jaundice. In September he had been admitted to another hospital for two and a half weeks after which he was discharged with the diagnosis of catarrhal jaundice. There had been no fever during this first hospital admission. Physical examination at that time had been negative except for the jaundice; and no abdominal organs nor masses could be palpated. He had been discharged as improving, the jaundice having been reported as disappearing and the stools as returning to normal color. He had returned to work for two weeks. Since that time however all symptoms have become steadily more marked.

The jaundice has been accompanied by very little pain except during the first few weeks when he had indefinite epigastric distress which he interpreted as gas pains because of relief with eructation of gas. He has had no severe colic.

On this second hospital admission in November, physical examination revealed a good general appearance except for the jaundice and the loss of weight. There were only occasional elevations of pulse and temperature. He did not appear toxic nor in any way especially ill except for the jaundice. He was mentally alert with no suggestion of impending coma. The liver was palpable three inches below the costal margin but normal in outline. The

gall bladder was not palpable and no other masses nor tenderness were found in the abdomen.

*Laboratory Findings:*

Urine—Essentially negative except for the marked amount of bile present.

There was no urobilin present.

Feces—Occult blood 3+++ . No bile present.

Blood examinations—

Count—Hgb. 60% or 8.7 grams, R.B.C. 2,500,000, W.B.C. 15,000.

Fragility Test—normal.

Icteric index—75.

Van den Bergh—Direct 9. Indirect 12.

Takata-Ara Test—3+++ .

Prothrombin time—markedly increased but this definitely responded toward normal under Vitamin K therapy.

X-ray—Gastric series was essentially normal.

*Differential diagnosis*—At this point our diagnostic problems can thus be defined as a decision as to the type of jaundice. Obviously this is not hemolytic but it could be intrahepatic or hepatogenous on the one hand or extrahepatic or obstructive on the other. Most of the laboratory data including the prothrombin response to Vitamin K favor obstructive jaundice, and therefore a surgical problem. On the other hand the positive Takata-Ara test suggests cirrhosis, but even an obstructive jaundice would be accompanied by gross secondary liver damage and cirrhotic changes after five months. Consequently we concluded that the positive Takata-Ara must be disregarded in this differential diagnosis.

In discussing the remote possibility of this case being one of hepatogenous jaundice, that is, a purely medical rather than a surgical problem, there would be three types to consider, namely, so-called catarrhal jaundice, acute yellow atrophy and biliary or peripheral cirrhosis. The long duration would seem to rule out the former two conditions; and operation in the presence of biliary cirrhosis although useless would cause little further damage. Whereas conversely further delay in the presence of obstructive jaundice might be disastrous.

*First operation*—After blood transfusions and Vitamin K therapy on December 7, 1943, under pontocaine spinal anaesthesia, the upper abdomen was explored. There was nothing abnormal in appearance on examining the abdomen except for a moderately enlarged gall bladder, and a moderately enlarged but otherwise normal liver. On palpation no stones were found in either the gall bladder or ducts, but on examining the duodenum for possible stone low in the common duct, a soft tumor was felt in the region of the ampulla of Vater. This was about 3/4" in diameter, and in shape suggested a button. The tumor seemed to be quite separate from the head of the pancreas. Without opening either the duodenum or the common duct we were reasonably certain of the diagnosis of carcinoma of the ampulla of Vater without gross metastases. It was obvious that a radical resection of the whole duodenum and half of the pancreas should be undertaken; but in spite of the recent trend toward a one-stage procedure we did not consider ourselves justified in attempting this after five months of jaundice. Our patient appeared to be in good condition, he had been well prepared with Vitamin K, and we preferred

to do the resection at this primary operation when he was completely free of adhesions, but it seemed quite a different matter to undertaking a long, severe operation after a few weeks of jaundice than after five months as in this case. Consequently a cholecystjejunostomy was done. A long loop of jejunum was brought up over the transverse colon to anastomose with the fundus of the gall bladder. On opening the gall bladder, as one would expect, only mucous or so-called "white bile" was found. The patient made an uneventful recovery and after three weeks the jaundice had practically cleared, as confirmed by an icteric index of 16.

*Second operation*—On December 28th the abdomen was opened under nupercaine spinal anaesthesia. The gall bladder with its anastomosis to the jejunum was adherent to the anterior abdominal wall immediately to the right of the incision where they were left undisturbed. The omental adhesions were cleared and the gastro-colic omentum was tunnelled by blunt dissection, in order to expose the whole anterior surface of the duodenum. The duodenum was mobilized by dividing the lateral peritoneal reflexion. The duodenum and head of the pancreas were then easily raised from the vena cava by blunt dissection. The stomach was next divided about two inches proximal to the pylorus; the pyloric region and first part of the duodenum were mobilized sufficiently to tie and divide the gastroduodenal and the superior pancreaticoduodenal vessels. The uncinate portion of the pancreas was dissected from the superior mesenteric vessels after isolating the middle colic vessels which arise high on the superior mesentery. This last manoeuvre necessitated tying and dividing the inferior pancreaticoduodenal branches of the mesenteric vessels. The mobilized duodenum was next divided proximal to the point where the mesenteric vessels cross it, leaving only enough duodenum to close. Resecting the intestine at this level is probably a mistake for removal of the whole duodenum, with the division beyond the mesenteric vessels makes the reconstruction easier due to the greater mobilization. At this stage the block of tissue being removed remained attached only by the pancreas and the common duct. By blunt dissection from above a tunnel was established between the portal vein and mesenteric vessels behind, and the body of the pancreas in front. With a finger through this tunnel as a guide, the pancreas was cut across. This caused the only real hemorrhage during the whole three-hour procedure, from moderate-sized vessels along the upper and lower margins of the pancreas. The pancreas was divided by a V incision so that the duct area would be well buried in the substance of the gland when the upper and lower margins were sutured together by interrupted black silk sutures. The dissection was completed by severing the common duct at the point where it passed behind the upper margin of the duodenum. More than  $1\frac{1}{2}$ " of duct was removed with the tumor.

The lower end of the stomach was anastomosed to the side of the jejunum between the Ligament of Trietz and the cholecyst-jejunostomy. This left only the common duct to be treated. The adhesions between the gall bladder and jejunum to the anterior wall made it technically difficult to anastomose the common duct into the jejunum. Consequently the cut end of the duct was sutured over and inverted with two layers of interrupted black silk. This again was probably a mistake which will be discussed later. A soft rubber drain was placed down to the region of the pancreas sutures. During

the operation a continuous gluco-saline intravenous was administered along with 500 c.c. of plasma.

*Post-operative Course*—During the first post-operative week the patient did unusually well. For four days the stomach was drained by Wangenstein suction through a Levine catheter, but after that he took fluids well and never vomited. For two days his temperature went as high as 101°, and pulse as high as 120 after which both settled down permanently. At the end of a week pancreatic secretion began to pour out around the drain, and three days later this discharge became obviously bile stained, showing that the sutures closing the common duct had been broken by the pressure in the biliary ducts. This copious discharge continued for three weeks but his general condition was kept up by supplementing his oral intake of food and fluids with daily intravenous therapy. But the discharge through this cutaneous fistula from the common duct and pancreatic ducts suddenly stopped just at the time we were deciding to operate a third time. In fact he was actually booked for this third operation. We had intended to anastomose the fistula into the jejunum or gall bladder. This suggested procedure seemed possible because of the superficial position of the latter structure, being adherent to the anterior abdominal wall and because of the close proximity of the fistula which penetrated the abdominal wall just medial to the adherent gall bladder.

After the fistula closed his recovery was quite uneventful. For a time abdominal cramps following food were common, and diarrhoea was somewhat troublesome, but he was discharged from hospital seven weeks after the second operation with no complaints and gaining weight very rapidly. He returned to his job as a baker at the end of four months. Ten months after operation he has gained thirty pounds, has no jaundice, and very little gastro-intestinal distress in spite of a relatively liberal diet. There is no diarrhoea. At present urine and feces examinations are essentially normal. The fat content of the stool is only 15% above normal and very few muscle fibres are seen. Blood count, blood sugar, blood urea, Van den Bergh test and icterus index are all normal.

### Discussion

Four problems arising in the course of this case probably deserve further comment.

- (1) Early operation is essential for jaundice with or without pain as soon as a reasonably accurate diagnosis of obstructive jaundice is established. How far can we carry the differential diagnosis before doing an exploratory operation?
- (2) If a radical resection is undertaken, should it be done in one or two stages?
- (3) If a two-stage procedure is chosen, what is the best method of managing the emergency jaundice problem at the first stage, in order to increase as little as possible the technical difficulties of the second stage?
- (4) Should an attempt be made to re-establish the pancreatic flow into the intestine?

The first of these four questions, the problem of diagnosis, has been discussed, but as a summary the following may be of some help. At present



these patients are practically all presented as jaundice cases. None of us like to do an unnecessary operation on such patients, but after a few weeks the milder cases of primary hepatitis usually known as catarrhal jaundice, have recovered; and after the same period the really severe ones, the acute yellow atrophy group, are either dead or so ill that the diagnosis is obvious; but if the case is sufficiently chronic to become a biliary or peripheral cirrhosis, although an exploratory may be useless, it will do little harm. Whereas on the other hand, delay of more than a few weeks<sup>4, 5</sup> in obstructive jaundice may mean missing the opportunity given by the early alarm signal of jaundice caused by a malignancy which has obstructed the common duct, before metastases have occurred. The question as to whether the jaundice is with or without pain, is only confusing. The often repeated statement that the jaundice due to a malignancy is painless, is not only doubtful but also misleading. For stones do cause painless jaundice, and on the other hand malignancies may cause considerable pain, even pain about the gall bladder due to the secondary stretching of that organ. And now that a malignancy in this situation can be resected, why try to distinguish these two conditions—both should have reasonably early operations and both require the full equipment that is necessary for any of these serious biliary tract operations. Just as pain is of little help in differentiation, so intermittency of the jaundice may be misleading as in this patient.

Laboratory confirmation of the type of jaundice may be a great help, but the temporary return of bile to the feces and urobilin to the urine should be watched as only a remission, as just mentioned. The finding of leucine and tyrosine crystals in the urine as found in the one small group is of course a real help, but liver function tests, hippuric acid, galactose tolerance, etc., are probably of greatest benefit in deciding whether to do a one or a two-stage operation rather than in deciding against operation. And finally as shown in this case the Takata-Ara test only demonstrates liver damage, but it does not distinguish whether primary liver disease, or secondary damage due to an obstruction. Probably the best laboratory criterion is the response of the prothrombin time to Vitamin K therapy. To summarize we can say—absolute diagnosis between extrahepatic and intrahepatic jaundice is often incomplete, but Vitamin K has completely reversed our attitude. Instead of not operating if in doubt we must now take the opposite view.

The second question, whether to do a one-stage operation or a two stage was difficult to decide. Recently the majority of surgeons<sup>6, 7</sup> have definitely preferred the one-stage operation on account of the difficulty caused by the adhesions produced by the first operation, and on account of the confidence arising from the aid of Vitamin K. However, after five months of jaundice this would seem to be a long severe procedure. If one has the opportunity of operating on a patient in good condition with a history of jaundice of from three to four weeks, a one-stage operation might certainly be easier.

The third point which I wish to discuss is the character of the first operation if two stages have been decided upon. Three alternatives have been presented:

- (1) As a first stage an anastomosis between the gall bladder and the jejunum is usually at least temporarily successful but the cystic duct may not be sufficiently patent to allow this by-pass to function;

and further such a procedure makes an anastomosis of the common duct into the jejunum definitely more difficult.

- (2) The common duct must eventually be united to the jejunum or a biliary fistula will result<sup>8</sup> because the pressure in the biliary tree is not sufficiently lowered by the by-pass to allow a ligated or sutured common duct to remain closed. Whereas the alternative of a primary anastomosis of the common duct to the jejunum is too difficult as a first stage.
- (3) For these reasons a third alternative as suggested by T. E. Jones<sup>9</sup> of Cleveland would appear to be the best choice for the first stage. He simply drained the common duct through a T-tube brought out through a stab wound in the side. This not only has no disadvantage such as interfering with the future operation, but rather facilitates the eventual union of the common duct with the jejunum. This last choice also overcomes the following practical problem in the management of such cases. It is generally recognized that all biliary tract lesions that have any suggestion of common duct involvement should be operated only in fully-equipped hospitals, but it is conceivable that a carcinoma of an ampulla of Vater might be found in an institution where the final operation could not be undertaken. A T-tube placed in the common duct at the first exploration would certainly be the ideal way around this difficulty.

The fourth and last problem to discuss is the re-establishing of the pancreatic flow into the intestine. It is absolutely true that the one most important factor leading to the accomplishment of radical pancreatico-duodenectomies was the realization that it was not necessary to have pancreatic secretion entering the intestine, and most patients have done well without this secretion. However, some have not done so well, and some have required pancreatic extract by mouth. Further, experimental work by Dragstedt suggests a more constant satisfactory recovery if at least some pancreatic tissue is left to secrete directly into the intestine.

To eventually discard what was at first considered the most important technical or scientific factor in a procedure is not a new phenomenon in surgical advance. Child, Cattell, Whipple and others<sup>10, 11, 12, 13, 14</sup> have all succeeded in re-establishing the pancreatic flow, but not without adding to the technical difficulties of the operation. Possibly this last advance is not to be advocated immediately, but it certainly must be watched.

### Summary

A case of successful removal of carcinoma of the ampulla of Vater has been presented.

Emphasis is placed on early operation for obstructive jaundice which acts as an alarm signal before metastases have occurred.

The choice of a one or two-stage operation has been discussed.

The alternative procedures possible as a first-stage have been outlined.

The eventual evolution of an operation to re-establish pancreatic flow into the intestine will probably be the procedure of choice in the future.

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# Penicillin

## A Review of the Literature\*

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I WANT to review some of the literature on Penicillin with you. As you know, Penicillin is a drug of remarkable therapeutic properties. It has saved many lives on the world's battlefronts and holds much promise as a therapeutic weapon for civilian needs. The production of Penicillin has gradually increased but it has by no means reached a level where everyone's needs can be supplied. The needs of the immediate military and war research must necessarily come first, but a limited supply is available for restricted use in civilian medical practise.

### *Historical*

Penicillin was discovered by the recently knighted Sir Alexander Fleming as far back as 1928. Fleming<sup>1</sup> recounts his discovery in a review of the subject. It is worth quoting him in part, verbatim

As one of the pupils of Sir Almroth Wright I had naturally been deeply interested during the whole of my career in the destruction of bacteria by leucocytes. During 1914-18 war I spent much time investigating problems in connection with septic wounds and I was impressed by the antibacterial power of the leucocytes contained in pus which exuded from septic wounds. It was also clear from these investigations that the chemical antiseptics in common use were more destructive on the leucocytes than they were on bacteria.

This interest in antiseptics and leucocytes was continued in post-war years, and in 1924 I was able, by a simple method, to demonstrate clearly the antileucocytic power of antiseptics, and to indicate that if the antileucocytic action of an antiseptic were greater than its antibacterial action, such antiseptic was unlikely to be successful in the treatment of a septic wound.

In 1922 I described lysozyme, a powerful antibacterial ferment occurring naturally in human tissues and secretions, in the white of the domestic hen's egg, and elsewhere.

In September, 1928, I was working on the variation of staphylococcus colonies following on a publication by Professor Bigger, who had shown that colonies of widely different appearance could be produced from a pure culture of an ordinary pyogenic staphylococcus. In the course of these observations culture plates of staphylococcus were examined at intervals with a dissecting microscope, which involved a temporary removal of the cover and exposure to contamination from the air. After examination, some of the culture plates were placed in an incubator and others were left to mature at room temperature. Further examination of one of the latter showed that a mould colony had developed towards one side of the culture plate. Such contamination with a mould was, in the circumstances, not unexpected, but what was astonishing was that in this particular culture plate the staphylococcal colonies for some considerable distance round the mould growth were obviously undergoing lysis. What had originally been a well-grown staphylococcal colony was now a faint shadow of its former self.

It is certain that every bacteriologist has not once but many times had culture plates contaminated with moulds. It is also probable that some bacteriologists have noticed similar changes to those noted above, but that, in the absence of any special

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interest in naturally occurring antibacterial substances, the cultures have simply been discarded.

It was, however, fortunate that, with the background I have briefly sketched, I was always on the lookout for new bacterial inhibitors, and when I noticed on a culture plate that the staphylococcal colonies in the neighborhood of a mould had faded away, I was sufficiently interested in the antibacterial substance produced by the mould to pursue the subject.

Fleming<sup>2</sup> in 1929 published a paper describing this chance finding. It was evident that a substance antagonistic to the bacteria had been formed by the mould and had diffused into the surrounding agar.

He therefore subcultured the mould for further study and found that broth in which it had grown for a week or two acquired marked inhibitory properties to many common bacteria. The mould belonged to the genus *Penicillium* and he later identified it as *PENICILLIUM NOTATUM* (Fleming 1932).<sup>3</sup> The active substance which is of unknown composition he christened "PENICILLIN." His crude product, the filtered culture fluid when diluted 500 to 800 times would completely inhibit the growth of staphylococci, and it was therefore some two or three times as strong in that respect as pure carbolic acid.

He made a number of antibacterial tests and found that the staphylococcus (*aureus* and *epidermitis*), streptococcus and pneumococcus were the most sensitive and *B. coli*, *B. Typhosus*, *Ps. pyocyanea*, *B. Proteus*, *V. Cholerae* and *Strep. faecalis* the least. *B. Diphtheriae* and *B. Anthracis* occupied an intermediate position. Different strains of *Strep. viridans* varied widely in sensitivity.

*B. pseudotuberculosis rodentium*, *B. pullorum* and *B. Dysenteriae* were as insensitive as the colon-typhoid group. The meningococcus and gonococcus were shown to be as sensitive as the Staphylococcus and *H. Influenzae* found to be insensitive. It was shown that staphylococci were not suddenly killed, but disappeared gradually over some hours, when in contact with penicillum.

There was apparently no toxic reaction when given intravenously to rabbits and mice or applied locally to the conjunctiva and to large ulcerated areas in man. A concentration which completely inhibited the growth of the staphylococci did not disturb the normal function of the leucocytes.

By 1932 Fleming<sup>3, 4</sup> had described the value of Penicillin for selective culture and as a dressing for septic wounds. The penicillin containing broth, had "certainly appeared to be superior to dressings containing potent chemicals." Its use as a dressing presented certain difficulties, because of the labour of preparation and the instability of the active principle.

Other workers attempted to isolate the active principle without success. A yellow pigment, chrysoygenin, which is presumably responsible for the color of the crude penicillin product was isolated (1932)<sup>5</sup> but was found to be inactive. Its value as a selective culture agent was consistently demonstrated and has been a standard procedure in many laboratories.

In 1938<sup>6</sup> Chain and Florey at the Sir William Dunn School of Pathology at Oxford prepared a plan for the systematic investigation of antibacterial substances produced by micro-organisms. It was thought that these might be chemically and biologically interesting, especially as many of them were active against pathogenic bacteria. Of a number of known antibiotics considered, "pyocyanae" and "penicillin" were chosen for the first investigation.

Penicillin was known to be unstable and therefore difficult to extract, but the fact that it was active against a range of important pathogenic organisms weighed the balance in its favour. It seemed worthwhile to see whether appropriate conditions could be found for extracting the substance, so that further examination of both its biochemical and biological properties could be made.

Chain and Florey<sup>7</sup> in 1940 reported their first anti-bacterial, toxicity and therapeutic tests. The tests were carried out with crude penicillin in the form of a brown powder, freely soluble in water, prepared from the culture medium. It is now known that this powder contained only 1 per cent to 2 per cent of pure penicillin.

In vitro tests showed that penicillin was not bacteriacidal but interfered with the multiplication of the bacteria. They found it inhibited the growth of *Cl. Welchii*, *Cl. Septique*, and *Cl. oedematiens* as well as the other organisms Fleming had noted. They found it to be non-toxic to mice and cats as well as human leucocytes. Penicillin in solution was absorbed from the intestines of rats and from the subcutaneous tissues and was excreted by the kidneys. It had a definite therapeutic effect on experimentally infected mice. It was noted that the mice infected with streptococci and staphylococci looked gravely ill for the first few hours, even when undergoing treatment, but thereafter recovered and were normal in 36 to 48 hours.

Abraham and Chain (1940)<sup>8</sup> described an enzyme which they named "penicillinase" which was capable of inactivating penicillin. This enzyme was present in the bacterial bodies of *B. Coli*, *M. lysodeikiticus* and an air bacterium which they identified only as a gram positive rod.

Gardener (1940)<sup>9</sup> reported that penicillin altered the morphology of bacteria when present in concentrations too small to inhibit growths completely. The principal changes appeared to be due to incomplete division, giving rise to swollen and grotesque giant forms and, in the case of bacilli and vibrios, to long filaments. Such forms would presumably be abnormally vulnerable to leucocytes and other defence mechanisms.

Penicillum might therefore be expected to have an effect "in vivo" at concentrations too low for complete bacteriostasis.

In 1941 Abraham, Chain, Fletcher, Florey, Gardener, Heatley and Jennings (1941)<sup>10</sup> reported further observations on penicillin. They discussed the growth of penicillin notatum and laboratory large-scale production; the methods of assay of the active substance; chemical methods for extraction and purification of penicillin; a fuller investigation of its bacteriostatic action and toxicity, and of absorption and excretions; and finally a report of the first therapeutic trials on man.

Before any trial was made on man, almost the full range of infections capable of response to the drug were known. Equally important was the knowledge that the upper limit of dosage was not likely to be influenced by any toxic effect. Laboratory work showed that oral administration of the unprotected drug would be ineffective because of its inactivation by the acid gastric juice; that frequent administrations would be necessary because of the rapid concentration and excretion of penicillin by the kidneys; that it would be unwise to prepare wounds for local application by cleaning with a number of common antiseptics because of the inactivation of penicillin by heavy metals and by oxidation. The lack of any inhibitory effect on

leucocytic activity by therapeutic concentrations of penicillin indicated that the disappearance of pus from lesions infected only by sensitive organisms would probably be a fair criterion of the elimination of sepsis.

The main points still to be elucidated when clinical trials were begun were: adequate dosage, frequency and routes of administrations and the most suitable methods for local applications.

The first human subjects treated by the Oxford workers were given penicillin intravenously in a "continuous drip" infusion of saline. The dose was injected 2 or 3 hourly. The first (case 1) was a febrile and severely emaciated man of 43 with a mixed staphylococcal and streptococcal pyaemia. He was treated for 5 days, after which penicillin supplies were exhausted, but during that time pus formation strikingly diminished and in some sites it ceased altogether and healing started. Appetite and general condition improved and the temperature fell. After 3 days more the patient was a febrile. Equally good results were obtained in a streptococcal osteomyelitis with septicaemia (Case 5). A large carbuncle resolved without discharging and without scar formation (case 3). A boy of 4½ (case 4), with a cavernous sinus thrombosis and lung abscesses due to staph. aureus, became strikingly better during 9 days treatment with penicillin, the cerebrospinal fluid becoming sterile after 6 days. He was afebrile and appeared on the road to recovery 4 days after the end of treatment when a cerebral vascular accident occurred, due to rupture of a mycotic aneurysm. At post-mortem the cavernous sinus region was occupied by granulation tissue, and in the lung also, healing was in progress. All that remained of the infection was small groups of cocci in microscopic areas of necrosis at the centre of the granulation tissue.

In an infant of 6 months (case 6) with a persistent urinary infection due to staph. aureus, penicillin was given by mouth with sodium bicarbonate (to neutralize the acid gastric juice) for 7 days. Though no penicillin could be detected in the blood, the urine became strongly bacteriostatic and the infection disappeared. Three patients with acute conjunctivitis and one with staphylococcal keratitis (case 7, 8, 9, 10) were treated by local application of penicillin. The symptoms were rapidly and strikingly relieved and a quick recovery took place.

Following the publication of this paper, work on penicillin began in many centres. Voluminous reports have been contributed notably in England and United States where the production of penicillin has reached a considerable and rapidly increasing scale. In each of these countries the output has been officially controlled, and supplies have been afforded for clinical trials only to chosen investigators.

### *The Properties of Penicillin*

Penicillin is an unstable acid, and the preparations used in therapeutics are its salts. The sodium salt employed for systemic treatment is hygroscopic and somewhat less stable than the more easily handled calcium salt, which is used for local application.

Potency is expressed in Florey (Oxford) units, an arbitrary amount determined by comparison with a standard preparation. (The potency<sup>12</sup> of penicillin preparations can at present be measured only by biological assay. Assay is carried out in vitro against a culture of a sensitive organism. As biological methods are subject to many variables it is necessary that each

assay should be a comparative measurement against a standard of known potency. Early in the work of Oxford, for the convenience of workers inside the laboratory, a purely arbitrary penicillin standard was adopted by which the unit was defined as that amount of penicillin contained in 1 c. c. of a certain buffer solution.

Dry preparations of partially purified penicillin have since been standardized against the original solution, and the "Oxford unit" (or "Florey unit") has been adopted as a standard of measurement by most workers in Britain, the U. S. A. and Canada. The potency of the unit is such that 0.01-0.02 of a unit per c. c. inhibits the growth of 26 sensitive strains of the staphylococcus.)

Pure penicillin would have a potency of at least 1000 units per mg.; that in present use is far from pure—owing to the serious loss of active substance which further purification entails and material with a potency of 100 units or less per mg. is quite satisfactory for clinical use. It has been shown experimentally that an increase in purity diminished toxicity, and clinical experience has shown that untoward effects such as pain on intramuscular injection and fever or thrombophlebitis following intravenous administration are caused mainly by products of low potency. Urticaria and contact dermatitis has also been reported<sup>13, 14</sup> (1944). These effects are thus due to impurities rather than to penicillin itself.

The laboratory plays an important role in connection with penicillin treatment. It is necessary first to determine the nature of the infections and the sensitivity to penicillin of the organisms concerned. Local treatment should be controlled by frequent further cultures. Systemic treatment calls for repeated estimations of the penicillin content of the blood in order to verify adequate dosage.

Penicillin has three properties required of an ideal antiseptic. It inhibits the growth of susceptible bacteria in extremely high dilutions; it has almost no local or systemic toxicity, and its action is unimpaired by serum, blood or pus.

At present the susceptible and the insusceptible organisms are essentially as follows<sup>14</sup> 1944:

#### Susceptible Organisms

Diplococcus pneumoniae  
 Streptococcus pyogenes  
 Streptococcus salivarius  
 Microaerophilic streptococci  
 Staphylococcus aureus  
 Staphylococcus albus (some strains)  
 Neisseria gonorrhoeae  
 Neisseria intracellularis  
 Actinomycoses bovis  
 Bacillus anthracis  
 Bacillus subtilis  
 Clostridium botulinum  
 Clostridium tetani  
 Clostridium perfringens (Welchii)  
 Corynebacterium diphtheriae  
 Vibrio comma

#### Insusceptible Organisms

Ebertheila typhora  
 Salmonella paratyphi  
 Salmonella enteritidis  
 Shiga dysenteriae  
 Proteus vulgaris  
 Pseudomonas aeruginosa (Bacillus  
 pyocyaneus)  
 Pseudomonas fluorescens  
 Serratia marcescens (Bacillus  
 prodigisus)  
 Klebsiella pneumoniae  
 Haemophilus influenzae  
 Escherichia coli  
 Staphylococcus albus (some strains)  
 Micrococcus albus (some strains)  
 Monilia albicans



Micrococci	Monilia krusei
Streptobacillus moniliformis	Monilia candida
Borrelia moryi (spirochaete of relapsing fever)	Blastomyces
Treponema pallidum	Mycobacterium tuberculosis
Leptospira icterohaemorrhagicae	Streptococcus faecalis
Spirillum minus	Brucella melitensis
Psittacosis virus	Plasmodium vivax
Ornithosis virus	Toxoplasma

The action of penicillin on bacteria is highly selective resulting in bacteriostasis and allowing the natural processes of the body to resolve the infection. Penicillin disappears rather rapidly from the blood after a single intravenous injection but a large percentage of the amount administered is found in the urine. When penicillin is given by subcutaneous injection—a variable route of absorption and not recommended—the concentration in the blood is less but a detectable amount is present for a longer period than after a single intravenous injection. Penicillin, when administered by any route, is found in a more concentrated form in the bile than in the blood serum, but the total amount excreted by the liver is small compared with that excreted by the kidneys. Penicillin is absorbed from the intestines when care is taken to protect it from being acted on by the acid of the stomach. Regardless of the method of administration, penicillin is found in the saliva in lower concentrations than in the blood collected at the same time. Tears, pancreatic juice and spinal fluid have no antibacterial activity when penicillin is given intravenously. Penicillin may be detected in the blood after it has been given by mouth along with adequate amounts of sodium bicarbonate.

When penicillin (1943)<sup>15</sup> is injected into inflamed body cavities such as a knee joint, a suprapatellar bursa or an empyema cavity, or when it is introduced into the cerebrospinal fluid, it may be detected in the blood and is found to be present for as long as twenty-four hours in the region into which it had been injected.

Fleming (1944)<sup>16</sup> has described a technic to determine the blood levels of penicillin that result from intravenous and intramuscular injection of different amounts of penicillin. He showed that the presence of leucocytes along with specific antibodies for the test organism added to the bacteriostatic power of the blood when penicillin was present. Thus he was able to explain why a favourable clinical result may occur even though penicillin cannot be detected by any of the methods available at present.

#### *Methods of Treatment (1944)*<sup>17</sup>

In the early clinical trials the greatest difficulty encountered was to find the adequate dosage. Eventually, after trial and error, a baby provided the foundation on which an adequate dose to eliminate infection was established as 1000 units per pound of body weight in 24 hours. Later, the more delicate slide—cell technique was adopted, in which the inhibition of bacterial growth by the blood serum could be accurately followed. This served to establish that intravenous or intramuscular injection should be repeated not less than 3 hourly, the standard single dose for an adult being 15,000 Oxford units (namely 5000 units per hour). It has been shown that even when nearly three times the dose is given, there is no prolongation of the time during which the drug can be detected in the blood stream. Good results have been produced

in acute infective conditions by much smaller dosage in the Mayo Clinic and elsewhere, but in general the above dosage should be used. It is felt that with inadequate small doses the organisms may become penicillin-resistant.

The INTRAVENOUS route often causes thrombosis at the site of injection after a variable period of therapy, although with good samples of the drug, the "drip" can often be continued at the same site for days.

The INTRAMUSCULAR route has been adopted for general use in the British and Canadian work. Most samples cause little general or local reaction, but some samples do cause prolonged pain after intramuscular injection. This reaction, the thrombosis after intravenous injections and other reactions of a minor character are due to impurities. By the use of the intramuscular route, material which causes a sharp rise of temperature on intravenous administration can be employed without causing a pyrexial reaction.

LOCAL administration has been used extensively in Britain and on the battlefronts, largely because of the scarcity of supplies, but many instances might be given where it has advantages over systemic treatment. Where an infection is definitely localized, and there is a surface or cavity which will retain a preparation of penicillin, a much greater concentration can be applied to the site of infection and, by using a suitable vehicle, the action of a single dose may be prolonged for as long as 24 hours. Treatment must be continued until all foci of infection have been removed. When dead tissue is present, surgical removal may be necessary, but radiological and bacteriological findings are better indications for this than the temperature chart.

Penicillin has proven valuable locally:

- (1) As a prevention of infection in wounds, enabling a potentially septic wound to be treated in much the same way as an aseptic one.
- (2) In the promotion of healing of burns and for ensuring the success of skin grafts.
- (3) In gas gangrene infections, especially in combination with antitoxin and surgery if necessary.

#### *Assessment of Progress*

When treating a case with penicillin, assessment of progress is liable to be based on the signs familiar in sulphonamide therapy. This may lead to erroneous conclusions. The temperature, for instance, in a case of osteomyelitis may assume a swinging character when penicillin is first given, and it never falls rapidly, as often occurs with the sulphonamides. By the time the temperature has become normal, which may take from 2 to 3 weeks, resolution has largely taken place. The radiograph, which in infections of bone show rapid and often startling rarefaction, should be regarded as evidence of the fast absorption of damaged bony tissue, and not of deterioration in the condition.

The earliest signs of progress are noticed by the Nursing Staff. Within a day or two the patient sleeps better, eats better and is relieved by much pain. If there is no diminution of bacterial growth within a week, consideration must be given to the advisability of aspiration or surgical interference in order to gain better access to localized lesions.

The blood count is also of value in assessing the arrest of infection. A steady fall of the leucocyte count to within normal limits and a rise in the erythrocyte count are indications that good progress is being made.

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# Abstracts From Current Literature

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DISEASES OF THE HEART. A REVIEW OF SIGNIFICANT CONTRIBUTIONS MADE DURING 1943. Williams, Conger.: Arch. Int. Med., 1944, 73:477.

Despite the war, special interest and work has been done in certain fields of cardiovascular disease, particularly in electrocardiography, congenital defects, arrhythmias, and hypertension. There are many problems relating to cardiovascular disease in war-time, which are of significance but which have not been published because of censorship or other restrictions.

May describes a new and simple clinical method of measuring venous pressure in the patient with cardiac disease. With the subject in the upright position, the veins of the under surface of the tongue are observed. Since the veins in the tongue lie about 200 mm. above the right auricle in the average patient, they will be collapsed with the subject erect unless the venous pressure is abnormally high, i.e., greater than 200 mm., in which case distention or venous pulsation has been noted.

Barker in an article on the mechanism of auricular paroxysmal tachycardia presents a summary of his ideas and those of others pertaining to the physiologic characteristics of this mechanism. He believes that the underlying mechanism of this condition is a circus rhythm in the auricles, the path of which passes through one of the specialized auricular nodes. In support of this belief he cites the following facts: There is evidence to show that the action of events outside the heart on the arrhythmia is concentrated on the specialized auricular nodes. Slowing of the auricular rate and termination of paroxysms are produced by vagal stimulation and by digitalis, and acceleration of the rate, by exercise. Further support of the theory of circus rhythm is found in the abrupt nature of the onset and termination of attacks, the remarkable stability of the rate, slowing of the auricular rate and termination of the attacks by quinidine. The occasional alternation in cycle length, is another point in support of the theory. He mentions several exceptions which cannot be explained by circus rhythm. In rare cases the rate slows gradually to normal instead of terminating abruptly. It is considered that these probably are not examples of true auricular paroxysmal tachycardia but rather represent an unusual and persistent type of sinus tachycardia.

Williams and Ellis report 36 cases of ventricular paroxysmal tachycardia collected from a series of 60,000 electrocardiograms. In all but 1 case organic heart disease was present. Toxicity due to digitalis was found to be the most frequent precipitating factor, with myocardial infarction next. It is emphasized again that the prognosis in such cases is that of the underlying heart disease. The use of chest leads as a valuable aid in the diagnosis of ventricular tachycardia is described. The chest electrode was placed in the third right interspace at the sternal border, and in several instances P waves which could not be seen in the standard leads were demonstrated. Since the diagnosis often depends on establishing the presence of an independent auricular rhythm, this procedure is considered to be of some value, except in cases of coexisting auricular fibrillation or auricular standstill.

## TREATMENT OF ARRHYTHMIA.

Sampson and associates present a good review of the present knowledge of the relation of administration of digitalis to potassium balance in the heart and add some observations of their own. In experiments carried out on a number of patients they showed that ectopic beats caused by digitalis could be abolished in every instance by oral administration of potassium salt, potassium acetate in a dose of 5 to 10 gm. They also studied the fasting potassium level of the blood serum and showed that there was no relation between that quantity and the presence or absence of ectopic ventricular beats. Furthermore, in a study of the curves of rise and fall of serum potassium in relation to the oral administration of potassium acetate, no significant differences occurred during administration of digitalis, even with toxic doses. Also, in many instances the serum potassium remained at fasting levels for a long period before ectopic beats again appeared. They suggested that lack of quantitative relationship between the serum potassium level and the occurrence of ectopic beats suggested fixation of potassium to cardiac muscle or alteration of the state of the muscle by potassium. It was believed that these findings offered positive evidence that the disturbance of potassium balance in the heart muscle is related to administration of digitalis.

Boyd and Scherf employed intravenous injections of magnesium sulphate in the treatment of 11 patients with paroxysmal arrhythmia, who included 2 patients with ventricular tachycardia, 8 with auricular tachycardia and 1 with auricular flutter. Injection of a 10 per cent solution of the drug was beneficial in three out of eight attacks, while a 20 per cent solution succeeded in eight out of eight attacks. The auricular flutter was not affected. As possible toxic consequences the authors cited increase of the PR interval and ventricular extrasystoles appearing for a short time following. No serious reactions were observed. However, the authors hesitate to use the drug in the presence of extreme myocardial damage, serious disturbances in auriculo-ventricular conduction or gallop rhythm.

In an article by Sturnick and associates, there is a report on the clinical use of a soluble quinidine preparation suitable for intramuscular injection. The mixture contains 0.15 gm. per cubic centimeter of quinidine, with a similar amount of antipyrine and 0.2 gm. of urea. The latter two drugs increase the solubility of the quinidine but have no other effect. The authors state that a search of the literature revealed no preparation of quinidine in sufficient concentration to warrant intramuscular use; the formula just given was obtained from the Cinchona Institute.

Their clinical observations were carried out on persons with a representative group of cardiac arrhythmias, including both auricular and ventricular tachycardias. From the results of their work, the following dosage is recommended. An initial amount of 0.45 to 0.60 gm. intramuscularly is considered the minimal effective dose. Response to each dose should be observed for one and one-half to two and one-half hours. If conversion to normal rhythm does not occur, the initial dose, or a slightly larger one, should be administered. This preparation is particularly valuable when absorption from the gastrointestinal tract is delayed or unreliable (in the presence of vomiting or shock) and when rapid therapeutic action is desired.

This type of quinidine preparation has been used at the Massachusetts General Hospital since its introduction by Riseman. Besides its use in the

situations already mentioned, it has proved of value for seriously ill patients in whom arrhythmias developed after thyroidectomy.

Gefter and Leaman gave 0.5 mg. of ouabain to 33 patients with rapid cardiac arrhythmias of auricular origin. They concluded that it is an effective agent for treating these disorders. No serious toxic effects were encountered, and the incidence of vomiting was low. Like digitalis, the drug was ineffective against simple tachycardias or in the presence of severe complicating infections.

Although there are reports of cures in isolated cases of subacute bacterial endocarditis following the use of sulfonamide compounds, with or without adjuncts, this method of therapy on the whole continues to be disappointing.

Lichtman submits a comprehensive report on a total of 704 cases, including 98 of his own and 606 from the literature. The average incidence of recovery was 5.5 per cent. The combination of fever treatment with chemotherapy appeared to offer the best possibilities.

There has been great interest in the possibility that penicillin might prove effective in the treatment of this largely fatal disorder. Studies with large doses are in progress and the results are much more promising than with smaller doses, but the duration of the follow-up is far too short for any adequate appraisal.

Loewe and associates report on a series of 7 consecutive cases apparently treated successfully with the combination of penicillin and heparin. Six patients had underlying chronic rheumatic valvular disease, while the other had a congenital cardiac lesion. *Streptococcus viridans* was the infecting organism in 5, hemolytic streptococci in 1 and pneumococci in 1. The daily dose of penicillin varied from 40,000 to 200,000 Florey units. The dose of heparin averaged about 200 mg. daily when given intravenously and 300 mg. every second day when given subcutaneously. The results indicated successful sterilization of the blood and relief of clinical manifestations, although admittedly further observations will be required before these patients can be pronounced cured. In no case was the total elapsed time since the beginning of treatment more than one year on the date of publication.

The efficacy of ligation of the patent ductus arteriosus in the treatment of subacute bacterial endocarditis complicating that condition is discussed by Touroff. He reports on a series of 11 cases subjected to operation after the complication of subacute bacterial endocarditis had set in. Two died from complications of operation, and 6 of the 9 survivors recovered without the benefit of chemotherapy. The 3 remaining patients did not recover, in spite of chemotherapy.

Further evidence is accumulating to show that recrudescence of rheumatic fever may be prevented by the use of sulfonamide drugs. The consensus among workers in this field is that the method offers definite promise.

Coburn reports his experiences with salicylate therapy in rheumatic fever. It is his belief that the inflammatory reactions of the disease can be suppressed by salicylate therapy, with resultant inhibition of pathologic changes in valves and myocardium. The factor of rheumatic infection is apparently not modified by therapy.

A simple method for the determination of the salicyl radical is described, providing more effective therapeutic control through measurement of blood levels of the drug. The intravenous use of sodium salicylate is advocated in the first stages of active rheumatic infection. Further evaluation is needed,

and the possibility of severe toxic reactions must be kept in mind. The drug may have a profound effect on body metabolism in larger doses.

Investigation of the problem of hypertension by the experimental approach, with special reference to the humoral mechanism of renal origin, continues to need follow-up.

Page and his co-workers have published a progress report of the experimental treatment of hypertension with renal extracts, in which the concept that renal ischemia is not essential to the production of hypertension is reiterated. Reduction of renal pulse pressure is thought to be a more essential mechanism. Improvement in the quality of renal extracts has been achieved, in that reactions have been reduced, but as yet the yield of active substance is low. An *in vitro* method for assay of renal extracts has been developed, which depends on the ability of the extract to destroy angiotonin. However, it has also been observed that with reduction in severity of reaction anti-pressor activity has also been lessened. The author still supports the concept of a humoral mechanism in which kidney substance, renin, interacts with renin activator to produce an effective vasoconstrictor agent, angiotonin.

In this article the authors state that clinical results obtained with the anti-pressor renal extract in 37 patients continue to be encouraging. Twenty-four of these had malignant hypertension, and 9 died. Reversal of changes in the eye-grounds with improvement of vision, reversal of the abnormal electrocardiographic picture to a more normal pattern and decrease in diastolic blood pressure with increase in cardiac output were the most striking changes in the group with malignant hypertension.

Lisa and associates describe the condition of the main renal arteries in 100 consecutive cases coming to autopsy at the City Hospital, New York. The differences in caliber between the sclerotic vessels in the hypertensive and non-hypertensive groups were insignificant, and the authors concluded that arteriolar sclerosis is a better index of blood pressure than the caliber of the main renal arteries. They believe that gross reduction of blood flow resulting from arteriosclerosis of the main renal arteries is of less importance than lowering of pulse pressure within the kidney.

The pioneer investigations of Castleman and Smithwick are of much importance. In the course of bilateral extensive splanchnic denervation (sympathectomy) done on 100 hypertensive patients, renal biopsies were made. This group included persons with all degrees of the hypertensive state, with changes in the eyegrounds varying from arteriolar narrowing or constriction without nicking (grade 1) to oedema of the optic discs with measurable elevation, usually accompanied by hemorrhage, exudate and other abnormalities (grade 4). Fourteen per cent of the subjects showed changes of grade 4. Insignificant or no vascular renal disease was evident in 28 per cent of the biopsies, and only mild changes occurred in an additional 25 per cent.

It was concluded that the morphologic evidence of renal vascular disease in more than half of the cases was inadequate to be the sole factor in producing hypertension, and that in many of these and probably others the hypertensive state antedated the renal vascular lesion, which, once established, probably aggravated the hypertension. Furthermore, these observations are not in keeping with the concept that renal ischemia due to preexisting renal vascular disease is the cause of essential hypertension in man.

An important approach to the present day treatment is surgical splanchnic denervation. The extensive operation of dorso-lumbar sympathectomy devel-

oped by Smithwick and previously reported has been in continued use by this author at the Massachusetts General Hospital in the treatment of hypertension. The details of this work are as yet unpublished, but the clinical results in select cases are impressive, with regard both to lowering of the blood pressure, systolic and diastolic, and to subjective improvement.

E. DAVID SHERMAN, M.D.  
Abstract Editor



## American College of Surgeons Announces 1944 Approved List of Hospitals

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The American College of Surgeons announces that 3,152 hospitals in the United States and Canada are included in the 1944 Approved List. The list is published in the annual Approval Number of the College Bulletin issued December 31.

A total of 3,911 hospitals were included in the 1944 survey and the approved hospitals represent 80.6 per cent. The first annual survey in 1918 included 692 hospitals of 100 beds or over of which only 89 or 12.8 per cent merited approval. Hospitals of 25 beds and over are covered in the current surveys.

A total of 2,342 hospitals of 100 beds and over were on the 1944 survey list, and 2,182 or 93.1 per cent were approved. A total of 1,119 hospitals of 50 to 99 bed capacity were under survey of which 789 or 70.3 per cent were approved. A total of 450 hospitals of 25 to 49 bed capacity were under survey of which 181 or 40.2 per cent were approved.

On December 31 of each year the ratings of hospitals under survey by the American College of Surgeons automatically terminate. The status of every hospital based upon all data collected from the current survey is reconsidered each year.

### FOR SALE

Doctor's residence at Freeport, N. S., with attached two-car garage, hot water furnace and all modern conveniences. The practice offers an excellent opportunity for a recent graduate to establish himself financially. Easy payments. If interested please write Dr. A. F. Weir, Freeport, N. S.

## Personal Interest Notes

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**D**OCTOR C. W. BLISS of Amherst attained his eighty-seventh birthday on the 21st of December last and we extend to him our hearty congratulations. Doctor Bliss is still vigorous and makes his regular calls upon his patients. He has been a resident of Amherst for some sixty years and besides his medical work he has always taken a keen interest in civic affairs.

In Middle Musquodoboit Doctor J. R. Cameron had a narrow escape from death. Answering a sick call at two o'clock in the morning of January 2nd, he drove his car from the garage and just as he turned from his own driveway to the highway, a large tree crashed on the car in a mass of branches and broken telephone wires. Doctor Cameron escaped unhurt but his car, purchased just two weeks before, was badly damaged, the radiator being completely smashed in. Had his car been two feet further ahead the full force of the heavy tree trunk would have crushed him in the car. The damage was heavy as the car was not insured.

### Surgeon Honoured

Surgeon Commander Harry S. Morton, R.C.N.V.R., son of Dr. C. S. Morton of Halifax, who was attached to the surgical staff of the Royal Victoria Hospital before the war, has been made a Fellow in the American College of Surgeons in recognition of surgical work in the Canadian Navy. Commander Morton, now stationed at Victoria, B. C., devised a new method of reducing broken necks, designed a portable orthopaedic table, and an original method of reducing and fixing fractures of the wrist and hand. Commander Morton is also a Fellow of the Royal College of Surgeons of England and of Canada.

Doctor W. Alan Curry of Halifax has also been made a Fellow in the American College of Surgeons, and is also a Fellow of the Royal College of Surgeons of England.

The BULLETIN extends congratulations to Lieutenant-Colonel James Arnold Noble, R.C.A.M.C., of Halifax and Wolfville, who was recently awarded the Order of the British Empire.

### To Engage Tuberculosis Specialist

Halifax's increasing war against tuberculosis gained further ground early in December with the decision of the Public Health and Welfare Committee to engage a tuberculosis specialist to serve as full-time medical superintendent of the Morris Street Hospital and to assist Health Commissioner Doctor A. R. Morton in developing a programme of modern control measures for the future. As a starting point in the stepped-up campaign against the disease, Doctor Morton favoured an immediate survey of school children, food handlers, factory workers and contacts of all known tuberculous cases. The committee

authorized him to endeavor to locate a suitable specialist and bring an appointment recommendation to the committee. He informed the committee that Doctor T. M. Sieniewicz, tuberculosis hospital medical superintendent on leave for war service, expected to return from overseas in the near future.

On the suggestion raised at a previous meeting that all cases at the Tuberculosis Hospital be treated free, Doctor Morton said such a practice would be impossible until the proposed addition to the hospital was at least under way. He also pointed out that free treatment for tuberculosis in force in Canada to-day was a provincial government undertaking rather than civic or municipal.

The Health Commissioner reported to the committee on a letter from Provincial Health Minister Doctor F. R. Davis, who expressed the opinion that in the matter of giving chest X-rays those who can afford to pay for them should do so. In Halifax, the letter pointed out, persons presenting themselves at the Dalhousie Public Health Clinic who needed such X-rays were sent to the provincially owned Victoria General Hospital where they were secured without charge. It was also possible, Doctor Morton reported, that persons requesting free chest X-rays could secure them at the office of Doctor J. J. MacRitchie, Provincial Medical Health Officer, for Halifax and Guysborough Counties.

Doctor and Mrs. D. F. Macdonald of Yarmouth were visitors in New York early in December.

The BULLETIN extends congratulations to Squadron Leader A. B. Crosby, R.C.A.F., and Mrs. Crosby, of Halifax on the birth of a son, Adam Brown Crosby, on January 6th; and to Dr. and Mrs. G. G. Simms of Pictou on the birth of a son, Jeremy Joseph Simms, on January 5th.

The marriage took place at Canning on December 30th of Phyllis Carmen Wescott, daughter of Mrs. Eleanor Wescott and the late Archibald Wescott, and Lieutenant Carrol Burnell Greene, R.C.A.M.C., son of Mr. and Mrs. Byard Greene, Pereau. Mrs. Greene graduated from the Children's Hospital, Halifax, and Lieutenant Greene from the Dalhousie Medical School in May, 1944.

### **Eighteen Hospitals Approved**

Eighteen hospitals in Nova Scotia have been awarded "full and provisional" approval by the American College of Surgeons for 1944, it was noted in a report of the annual survey released January first by Associate Director Malcom T. MacEachern, M.D. Five of the hospitals have accepted the minimum requirements and are endeavoring to put them into effect, the report said, "but for lack of time or other acceptable reasons have not been able to do so in every detail."

Approved hospitals in the province are:

Amherst, Highland View Hospital, minimum requirements; Antigonish, St. Martha's Hospital; Dartmouth, Nova Scotia Hospital; Glace Bay, Glace Bay General Hospital, St. Joseph's Hospital; Halifax, Camp Hill Hospital, Children's Hospital, minimum requirements, Grace Maternity Hospital, Halifax Infirmary, Halifax Tuberculosis Hospital, minimum requirements, and Victoria General Hospital; Kentville, Nova Scotia Sanatorium; New

Glasgow, Aberdeen Hospital, minimum requirements; North Sydney, Hamilton Memorial Hospital, minimum requirements; Sydney, City of Sydney Hospital, St. Rita's Hospital; Wolfville, Eastern Kings Memorial; Yarmouth, Yarmouth Hospital. Victoria General Hospital in Halifax is also approved for training internes by the Department of Hospital Service of the Canadian Medical Association, the report said.

The marriage took place in Annapolis Royal on December 26th, of Miss Elaine Borden Dickie, grand-daughter of the late Doctor B. C. Borden and Mrs. Borden of Mount Allison University and Surgeon-Lieutenant David Lloyd MacIntosh, R.C.N.V.R., son of Rev. and Mrs. M. H. MacIntosh of Waverley. Mrs. MacIntosh, who has been on the teaching staff of Sir Charles Tupper School, Halifax, graduated in Arts from Mount Allison University and in Education from Dalhousie University. Surgeon-Lieutenant MacIntosh has been on active service for several years. He graduated from Dalhousie Medical School in May, 1939, and prior to enlistment was on the staff of Toronto General Hospital.

The BULLETIN regrets to learn of the illness of Doctor H. W. Schwartz, the Editor-in-Chief of the BULLETIN, who has been confined to his house for the past three weeks. We also wish to extend our sympathy to Doctor G. L. Covert, who has been on the sick list for about a month. We understand that Doctor Covert has made an excellent recovery and will be back in practice within a short time.

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## Correspondence

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2 Canadian Field Hygiene Section  
1 Canadian Division  
Canadian Army Overseas, C.M.F.  
November 10, 1944

Dr. H. G. Grant  
Secretary of The Medical Society of Nova Scotia  
Halifax, N. S.

Dear Doctor Grant:

It was indeed a pleasure—a pleasure with a “lift” in it—to receive your good message of August 2nd from The Medical Society in session at White Point Beach. It is a sustaining comfort to many of us in this and other theatres to know that we are backed by the good wishes and continued interest of fellow practitioners at home.

With the Season's Greetings

Sincerely yours

(Sgd.) Sid Gilchrist

## Obituary

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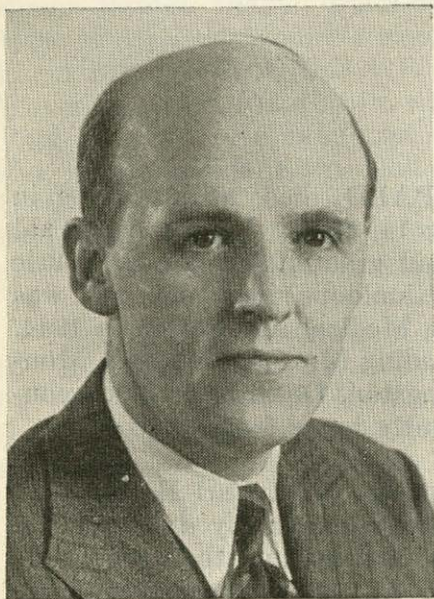
**D**OCTOR MATTHEW GEORGE ARCHIBALD died at his home in Kamloops, British Columbia on December 14, 1944. Doctor Archibald was born at Middle Musquodoboit in 1873 and graduated from Dalhousie Medical School in 1898. He had practised at Kamloops since 1905, and was made an honorary life member of the Canadian Medical Association in 1944. Surviving are his widow and five children, including Mrs. H. E. Rand, Montreal, Corporal G. D. Archibald, R.C.A.F., Kingston, Ontario, and Surgeon-Lieutenant W. S. Archibald, R.C.N.V.R., recently home from overseas.

The BULLETIN extends sympathy to Major and Mrs. Carl R. Trask of Yarmouth on the death of their six year old son, Stephen, by drowning, on December 18th. It is believed the boy stumbled and fell into the water while throwing stones into the harbour. Major Trask is at present overseas with the Canadian Army Medical Corps.

The BULLETIN also extends sympathy to Captain Allan S. MacIntosh, R.C.A.M.C., at present in Belgium, and Surgeon-Lieutenant David L. MacIntosh, R.C.N.V.R., at present in Toronto, on the death of their father, Rev. M. H. MacIntosh, who died at his home in Waverley on January 5th, at the age of seventy-six.

## "Accent on Research"

### Among Post-War Plans of New Company



Walkerville, Ontario: An appointment of interest to the profession was announced recently, when Gordon Gray was elected Vice-President and General Manager of Whitehall Pharmacal (Canada) Limited. This completes the organization of the new company which will continue to manufacture and distribute such products as Anacin, Kolynos and Bisodol.

Centralization of Research and Control laboratories has already been accomplished, according to Mr. Gray. He states:—"These essential activities are being maintained and expanded so that the standards of purity and quality of Whitehall products will be unsurpassed."

In recalling the circumstances under which Anacin was originated—the tragic epidemic of influenza during World War I—Mr. Gray points out that, ironical though

it may be, the adversity of war has always resulted in scientific advancement. From this war, salutary improvements in therapeutics can be expected, and, pharmaceutical laboratories are already speeding work on new products.

Whitehall Pharmacal is assuming an important place in these research activities and the stated aim of the new organization is to constantly fulfil its responsibilities to the public interest.

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### Vitamin Advertising and the Mead Johnson Policy

The present spectacle of vitamin advertising running riot in newspapers and magazines and via radio emphasizes the importance of the physician as a controlling agent in the use of vitamin products.

Mead Johnson & Company feel that vitamin therapy, like infant feeding, should be in the hands of the medical profession, and consequently refrain from exploiting vitamins to the public.