Drugs as They Affect the Circulation*

D. S. Lewis, M.D.

Montreal

OUR first knowledge of the circulatory system, in the modern sense, may be said to date from the time of William Harvey. He was the physician of Charles the First. This will place hm in his proper historical setting. The time of his great work was that of the English Civil War and John Milton. His discovery of the circulation of the blood carried our knowledge as far as the heart, arteries and veins. Having no microscope, further progress had to wait for thirty years until the discovery of the capillaries by Malpighi and Lowenhoek completed the cycle of the blood stream.

About a hundred years later there was another period of great activity, again associated with wars and this time the French Revolution. Auenbrugger described percussion (1761), Priestley discovered oxygen (1772), Withering digitalis (1785), and Laennec the stethoscope (1816). These discoveries made possible the present era of clinical medicine.

Then followed a further period of one hundred years when most of what Withering had discovered was lost track of, until, at the beginning of the twentieth century, the appearance of Mackenzie, the introduction of the electrocardiograph, blood pressure readings and the renewed use of digitalis, once more set the management of heart disease on the forward way.

The past twenty years have been spent in correcting many of the minor errors and also filling in the blanks. Our knowledge of the arterioles and capillaries has made great strides thanks to the work of Sir Thomas Lewis and Krogh. The contributions of the chemists and physiologists to water balance, the regulation of blood pressure, and the role of the adrenals in the control of shock have opened the way for the considered use of many of the cardiac remedies.

Drugs affecting the Circulation

Any complete list of the drugs affecting the circulation would be unending. Indeed Cushney in his book *The Digitalis Bodies* lists twenty-one as having a digitalis action. Many of these became known by their having been used as ordeal or arrow poisons by aboriginal peoples.

List of Principal Drugs According to Their Action.

Direct Action

HEART: **Force**: Digitalis: Strophanthin.

Rhythm: Digitalis, Quinidine, Mecholyl, Sedatives.

Coronary: Nitrites, Xanthines (Theobromine, Theophyllin, Aminophyllin)

Nutrition: Glucose, Vitamins, Thyroid.

*Paper delivered at the annual meeting of The Medical Society of Nova Scotia, Kentville, N.S., July 7, 1943.

Adjuvants

Diuretics: Mercurials, Xanthines.

Respiratory Centre: *Depressant*: Opium, Barbiturates.
Stimulant: Aminophyllin, Coramine (Nikethamide).
Replacement: Oxygen.

Blood Pressure: Benzedrine (Amphetamine) etc.

From this large number I propose taking only one or two for discussion to-day.

Digitalis

Digitalis and its near relatives are of interest from a chemical point of view. They all have a pentenophenanthrene nucleus. This nucleus keeps turning up all through pharmacology. It is the basis of the various forms of Vitamin D. It is the central figure in the various sex hormones and the hormones of the adrenal. Slight additions to this nucleus make all the difference in the results produced by these apparently unrelated bodies.

Mode of Action of Digitalis

This is one of the places where science repeatedly has had to retrace its steps. Pharmacologists at one time believed that the vagus action was the great medium for the production of digitalis effects. Now almost the whole effect is credited to the direct action of the drug on the heart muscle. Experimental studies would suggest that digitalis increases the efficiency of the heart muscle to a notable degree, so that the same degree of effort produces much greater results. The supporters of this theory on digitalis action believe that all the effects which follow the use of digitalis in heart failure are secondary to this primary action. The slower heart rate, the fall in venous pressure, the increase in cardiac output and the disappearance of cardiac dilatation all result from this direct action on the heart muscle. According to Gold, even the so-called vagus stimulation results from an improved circulation.

Of course with poisonous doses the medullary centres are affected, notably the vomiting centre, but these are not therapeutic actions. Some however claim for digitalis a sensitising effect on the receptor fibres of the carotid sinus, and this may play a role in the production of the drug's action.

Effects on the Conducting System

Another effect is on the conducting system. This conducting system consists of a modified type of muscle; it shares with the rest of the cardiac muscle in the stimulating effect. This stimulation produces an increase in the refractory period, which plays a definite role in the reduction of the rate in auricular fibrillation. The vagus effect is not an active factor here, unless the drug be used in large doses.

The Peripheral Vascular System and the Kidneys

Digitalis has no direct effect on either the peripheral vessels or on the kidneys.

Changes in the Electrocardiographic Tracing

Digitalis can reproduce almost any type of electrocardiographic abnormality except intraventricular conduction defects, according to Goodman and Gilman. This should be kept in mind when tracings are being read. The most frequent change is the one seen in the ST interval, leading to a diagnosis of coronary artery disease with its fear of sudden death. The history of treatment should always be sent along with the patient to the electrocardiographer. The amount of digitalis required to produce the changes need not be large. The results of a wrong interpretation of the tracing in terms of a patient's happiness and activity, may be great.

The Indications for Digitalis

There are two or three indications for the use of digitalis.

First: The presence of heart failure with congestion, and

Second: The presence of auricular fibrillation and auricular flutter.

Third: Paul White adds one more: To ward off impending failure in older persons with dyspnoea on exertion or in cases of emphysema where the dyspnoea on exertion is greater than the pulmonary condition would suggest.

This is an almost complete reversal from the teachings of Sir Thomas Lewis who thought that auricular fibrillation was the only definite indication.

Contraindications for Digitalis

These are of interest and at times of importance. Speaking generally there are no contraindications to the use of digitalis. In this positive age there are only indications. If the indications are absent, there is no need to give the drug. Reasons of economy should prevent its unnecessary use. Yet it is said that digitalis is one of the most commonly misused drugs. About eighty percent of its use is unnecessary. However for those of us who like definite directions the following contraindications are noted:

Digitalis is a dangerous drug in the acute stages of coronary thrombosis. It is useful in the later stages of the disease if congestive failure makes its appearance. Given in full doses in an attempt to control the tachycardia of the acute attack, it will augment the irritability of the heart muscle and definitely increase the chances of ventricular fibrillation and sudden dealth.

In diphtheria it is definitely contraindicated unless congestive failure is present. Its use should be cautious even then. Levine and Cecil have shown that auriculo-ventricular or intraventricular block are often present. Why then give a drug that tends to increase this damaged cardiac function still further?

It will not control the tachycardia of Effort Syndrome or "Soldier's Heart", of fever, or of thyrotoxicosis. In the first two it is harmless though useless, in the last many believe it may give definite trouble.

In acute rheumatic carditis the results are so disappointing that its use even in the presence of fibrillation is discouraging.

So also in the transient outbursts of auricular fibrillation in the arteriosclerotic heart, its use should be delayed until congestive failure makes its appearance. Lewis states that too early use tends to perpetuate the fibrillation, which often passes off if left to itself. Quinidine is the drug of choice if any drug is used. On the other hand if the attacks come frequently and repeatedly,

and quinidine does not control them, Eggleston rather inclines to the use of digitalis for the very purpose of making the condition permanent, continued fibrillation being more easily borne by the patient than the recurring attacks of fibrillation. So also with recurring attacks of heart block. Digitalis will tend to make the block constant with an increased degree of comfort for the patient.

Digitalis is useless in peripheral vascular failure and shock: also in the presence of the acute infections such as pneumonia, where as Meakins has shown, the prime factor is peripheral vascular collapse rather than cardiac failure.

Dosage of Digitalis

Fashions change in the dosage systems employed with digitalis just as they do in infant feeding. From Withering's generous doses, we passed through the stage of the homeopathic doses of the 1890's to the medium doses of Mackenzie and on to the saturation system of Eggleston. Some clinics favour the massive doses while others use more conservative methods. There are two things that should guide us in the choice of method.

First: Is the patient so seriously ill that urgent measures are required? and Second: Is the patient so located that he can be observed during the administration of the large doses? If both answers are in the affirmative then the large doses may be employed, if not then the more conservative levels should be employed. From the above you will see that in ordinary practice the conservative doses will be the ones most frequently employed.

In a general way a person of average weight is saturated by 1.5 gms. (gr.xxiiss.) of the powdered digitalis leaf given during a period of 24 to 36 hours. This is the total dose. It should be divided into four or five parts and one part should be given every six hours until the desired effect is produced. The first dose should be given in the morning, and the patient can then be under observation during the day in case untoward signs make their appearance. These signs are nausea, loss of appetite, extra-systolic arrhythmia, or mental disturbances.

For maintenance purposes the dose will vary from patient to patient. It is arrived at by a system of trial and error. The average amount will be from one and a half to two grains daily, but it may vary from one half to four and a half grains. The pulse rate and feeling of well being should be the guide. In certain cases the higher doses will be required to allow of activity without undue rises in pulse rate.

It is generally agreed that the intravenous or intramuscular routes are rarely needed. If speed of action is required it can usually be attained by the massive oral doses. The drug is absorbed relatively slowly from the digestive tract so that from four to six hours are needed for the development of full action of a dose by mouth. The intramuscular injection produces its effects in half an hour. Again the dosage by injection is only about one tenth of that required by mouth. This difference is explained by the imperfect absorption of the digitalis from the digestive tract. Nativelle's Digitaline (Digitoxin) is the only preparation which has the same dose by mouth as by vein. It is fully absorbed by the digestive tract.

For patients who cannot be given the drug by mouth the rectal route is quite satisfactory. The level of dosage is the same as by mouth.

Standardization of Digitalis

The strength of digitalis is now laid down by the Pharmacopoeia as ten international units per gram. Transferred to the Imperial System.

I International Unit = 1½ grs. Powdered Digitalis
= 1/600 gr. (0. lmg) Nativelle's Digitaline
= 1/160 gr. (0.4mg) Digoxin (B.W. and Co.)
= 1/200 gr. (0.33mg) Digilanid

While this standardization represents a great improvement over conditions ten years ago, one should always be on the guard for errors in strength. For example in one of the large hospitals in Montreal a small outbreak of digitalis poisoning was traced to a batch of tablets which were later found to be 50% over strength. Conversely an absence of response should also be watched for, as weaker tablets occasionally make their appearance.

The Tincture of Digitalis is subject to a good deal more variation in strength and also to the hazards of the patient measuring the drops with a dropper. These drops are never the same size even from a standard dropper. The tablets have largely superseded the liquid preparations.

Here is one place when the maker is an important factor. Do not save money by using an inferior brand. Another point is that the tablets with ordinary care do not deteriorate. Keep the bottle stoppered.

The Coronary Circulation

The other drugs which we might consider are those which affect the coronary circulation. The ones which act in the acute phases of angina—amyl nitrite and nitroglycerine are so well known that they require little comment. Remember that the coated nitroglycerine tablets are not nearly as effective as those of the hypodermic type. They should always be used under the tongue; never swallowed.

A group of drugs frequently used for their coronary effect are the so-called xanthine derivatives. Their ability to alter the coronary flow has often been questioned. Clinical trail has been used in England to prove that placeboes (lactose for example) give as good results in well controlled cases. Recently laboratory experiment has seemed to indicate that aminophyllin might have some power of increasing the coronary flow, but others claim that the increased flow only appears after general myocardial stimulation has occurred. Levy Bruenn and Williams appear to have proved clinically, that aminophyllin given intravenously has a definite effect in postponing the pain in the angina of effort, but taken by mouth its effects are much less striking, but their series of cases was too small to carry much weight. Taking a broad view the Scottish verdict "Not proven" would seem to apply.

However these drugs are great clinical favourites. Gunn, the English Pharmacoligist, has remarked that very few subjects of cardiac pain have escaped exposure to one or other of this group of drugs. Taking it all in all you will each be guided by your own experience.

More noticeable results are reported from the use of testosterone in older patients with the angina of effort. The remedy has had quite definite effects in relieving seizures both temporarily and, in a smaller number, for a much

longer period. It is more effective in males than in females. The dose required is relatively small.

There is one place where aminophyllin is quite worth a trial. It is at times outstanding in its effect on Cheyne Stokes respirations. No one who has had anything to do with such a case will fail to be impressed by the results which follow its intravenous use. The relief is usually of a temporary character but it occasionally lasts several hours. Its use is worth remembering. Of course the outstanding sphere of usefulness of aminophyllin is for the relief of asthma which has become resistant to adrenaline. It is also an excellent diuretic in cases of passive congestion of purely cardiac origin.

Conclusion

There are many other drugs which might be touched upon but under the limitations of the programme it seemed best to deal with one or two thoroughly rather than to cover a larger field. It is by knowing a few drugs well and understanding their effects thoroughly that one can get the most out of drug therapy. This knowledge will make the medical man less the trusting disciple of the itinerant salesman and more the careful physician "Proving all things and holding fast that which is true."

Some Observations on Peptic Ulcer*

NORMAN H. GOSSE, M.D.

THE subject of peptic ulcer, important enough in the past, is coming in these hectic days to assume a place of increasingly greater importance. The stresses and strains upon the nervous system which our own present accelerated pace involves provide one factor, food defects and deficiencies will continue to constitute another, and it is not unlikely, from evidence already to hand, that we shall have to be prepared for a much higher incidence of such cases among those returning from direct participation in the activities of war.

From present knowledge however, one cannot say how much war itself has contributed, but one fact that has emerged from war-time study of the subject is that there was a greater amount of peptic ulcer in the civilian population before the war than was ever suspected, and that of the many cases being diagnosed in the armed forces by far the most of them gave a history of symptoms of long duration. These facts, and the fact that I have myself been seeing more and more of them of all shades and degrees is my apologia for this effort.

The subject, however, is so large that no one could hope to cover it in a single paper of reasonable length. This will be confined, therefore, almost entirely, to the management of such cases and to such phases of the subject as bear upon that.

The old idea of an Ulcer Type of person—the person of "long narrow habitus", the Cassius type "with lean and hungry look",—did very good service in making us suspect ulcer, given certain symptoms; but unfortunately, we have been much too logical, and have argued that the same symptoms in another person could not be ulcer because he or she was short and fat. We have also been disposed to look for duodenal ulcer in men, and gastric ulcers more in thin women, and to regard all the "fair, fat, flatulent, females of forty" as subjects only of gall-bladder disease. Now I would not have you throw away those ideas altogether, they will frequently point to the truth; my point is, that those beautiful sounding phrases are not entirely trustworthy. They should be expected more frequently to let you down. I recently had referred to me a heavy, thickset, flatulent man of forty-four. He was a good gall-bladder type and had some gall-bladder symptoms, but he had a duodenal ulcer. A short time before a woman of about the same age gave a history of having had her appendix out three years before for certain symptoms and her gall-bladder out a year later for the same symptoms. The symptoms persisting, she was now to have her first gastro-intestinal examination, and this showed a chronic duodenal ulcer. She was quite short and plump and as stated, was in her middle forties. Isn't it strange that the "chronic appendix," the gall-bladder and the duodenal ulcer should have produced identical symptoms?

Having gone through the throes of adequate investigation then, and having arrived by nice scientific processes at a proper estimate of the case how are we going to decide upon its management?

It is necessary, at this point, to differentiate between gastric lesions on the one hand and duodenal lesions on the other. In the case of gastric ulcers even

*Read before the Cape Breton Medical Society, May, 1943, and resection cases herein reported shown before Dalhousie Refresher Course 1943.

the more conservative elements in medical opinion agree that this is the more serious lesion and that while in small uncomplicated ulcers a medical regimen should at first be followed, in all others, and in those if they do not promptly heal, surgical measures are to be resorted to promptly.

We are coming more to the view that gastric ulcers do not heal as readily as we used to teach, that the incidence of cancer occurring in ulcer, together with *The number of cancers which are given a roentgenological diagnosis of ulcer*, is much greater than has been thought, and therefore, that danger to life in prolonged medical treatment is much greater than that incident to the operation of gastric resection.

The result of this is found in the fact that in the greater clinics of this continent to-day sixty to seventy-five per cent of gastric ulcers are operated upon, and it is interesting to note that about ten per cent of those operated upon as gastric ulcers are found to be gastric cancers.

Duodenal Ulcers

When we consider duodenal ulcers a different story is to be told. At the time of my initiation into the mysteries of medicine, the practice seemed to be to do a gastro-enterostomy on them all. This practice was as scientifically unsound as it was found to be clinically unsatisfactory, in very many cases. Then arose the great issue as between Medical and Surgical treatment,since which time we have learned a very great deal. At least Surgery has learned a very great deal; and though I know that Medicine has also yet, I have reason to question whether it has in this realm as much as it really should, and if it has, why its knowledge is not better promulgated.

I mentioned that gastro-enterostomy was at one time the treatment of choice. Then came the Sippy treatment and Surgery stepped back while, for a considerable time that method—which was a really great advance—held sway. Its now obvious defects, chief of which are excess of alkali and deficiency of certain vitamins, caused it to go by the board, or at least to be so profoundly modified as to be unrecognizable.

The treatment which replaced the old Sippy treatment respects the following principles:

1. Bland, fluid or semi-fluid foods during the healing period, frequently given.
2. The maintenance of or increase of weight, in the average case.
3. The use of anti-spasmodics.
4. Adsorbents for excess acidity.
5. Appropriate laxatives.
6. Adequate psychic control.
7. Exclusions of poisons.
8. X-ray and Lab. control.

A word or two on each of these; We have used methods of feeding planned by different persons or groups, and generally speaking find that of Hurst to provide a satisfactory basis for treatment both as to amounts and time of giving them. The factors that make modification necessary we are not so sure about. It is possible that if we did careful basal metabolic readings on them

all some help might emerge. The fact is, however, that under conditions that appear to be exactly the same, one loses while the other gains weight on the same number of calories. Clinically, this is easily met by weighing the patient frequently; and for those who are losing, by substituting cream for milk, in as many feedings as may be indicated, considering the rate of weight loss and the degree of attenuation of the cream. In the treatment of the average ulcer case, weight loss must be changed to weight gain. In the case of some of the fat ones, however, it would simplify matters if the milk vendors were even less scrupulous than they are sometimes said to be.

3. *Anti-Spasmodics*: This writer is satisfied that there is no real substitute for atropine, but, the exigencies of our time frequently demand that some substitute be employed. Several of those suggested by different manufacturers have been exhibited by us and some of them have been found wanting. Syntropan seems to us to be the best of them.

Perhaps under this heading should come the matter of gastric lavage. If there is gastric retention or dalay in emptying how much is spasm or oedema, and how much true organic obstruction, is at first by no means clear. We believe that the part played by lavage in the relief of such obstruction is a very important one. Its nightly use during the early days of treatment will, in some cases of obstruction show that such obstruction is not organic or not entirely so.

4. *Adsorbents:* The sippy powders as neutralizers have long since given place to adsorbents. First came the aluminium jels and then magnesium trisillicate. Today they are running along side by side, and operate in the same way. The trisillicate is a trifle cheaper, and in the majority of cases it will prove perfectly satisfactory, but every now and then it will be found a bit irritating. Because of this, some clinics use nothing but aluminum hydroxide, which seems to have no irritating properties.

5. *Laxatives:* Unfortunately, there is one fly in the ointment which soothes the acid stomach, albeit a very small one. Adsorbents adsorb more than acid. At least the net result, in most of those who take them, is constipation. It is usually found that F. E. Cascara given nightly in adequate doses is well tolerated, and gives satisfactory results. The olive oil,—or as we now have it, the cotton-seed oil or the corn oil—of our treatment is, however, sometimes laxative enough.

6. *Psychic Control:* Unless this is effected at the beginning of treatment, and unless there is reasonable hope that it will be maintained both in the immediate and remote post ulcer stage, it will be better to let some other person conduct the treatment. The relationship between the psyche and the intestine would seem to be closer than the psyche and sex, Freud to the contrary notwithstanding. We see it beautifully illustrated in the condition of chronic ulcerative colitis, when, any emotional or nervous upset precipitates the condition anew. We see it again here in the difficulty of getting good results in the treatment of peptic ulcer, whether the treatment be conservative or radical.

The following represents one type of this: A short while ago I was carrying along two men who were lying in rooms almost opposite each other on one of the corridors of a Halifax hospital. Each had a duodenal ulcer, of very similar roentgenological findings. One was a man of sixty, of "nervous type", but sensible and fully co-operative—a good patient. The other was fifty, also a man, fat, of central European birth, with much more money than the other

but a complainer and a worry-wart who never really accepted the discipline which his treatment demanded. The first of these, who should, by ordinary standards, have been the worse, had an uneventful and rapid recovery, a roentgenological cure, left the hospital in four weeks and remains symptom free. The other gave a most unsatisfactory result and is still complaining though he has since visited the Montreal savants, with equally unsatisfactory results.

7. *Poisons*: *Focal Infections* which used to figure so prominently do not have quite the same importance attributed to them. It would seem to be right, proper, and important to clean up foul mouths, but upon the importance of less obvious foci elsewhere, the verdict "not proven" will have to be given. It is significant, however, that the common cold may be the immediate precursor of a recrudescence of the ulcer.

Alcohol and Tobacco: Alcohol which has ordinarily been severely censured and proscribed though still proscribed is not now regarded as being as serious a deterrent to the healing of an ulcer as is tobacco. Definitely in our cases they do better with tobacco interdicted, and a paternal government is seeing that we shall come to no harm from what alcohol we get.

8. *X-Ray and Lab*: The first of the criteria of healing that we look for is freedom from symptoms. That is important, but, especially in the case of duodenal lesions, in which remissions in the symptoms are to be expected, even in untreated cases, is not reliable if taken alone. We must have some other guide. Our practice is that if symptoms settle down promptly and remain down, we x-ray them in three to three and one-half weeks. The majority will be shown to have the crater reduced or no longer in evidence and to have normal emptying time. There should be no occult blood, and in the average case there should be moderate gain in weight. From this point the diet becomes more varied. They are kept under close observation for a few days on the larger diet and are then allowed to leave the hospital on a more liberal but still restricted regime. The minority must be continued on the strict regime and checked again at a later date.

Up to this point I believe our pure internist will go with me. From this point however, it seems to mean, so often, the parting of the ways. What then is the relationship of surgery to this condition as we see it?

Miller divides the indications for surgery into *Absolute Indications* and *Relative Indications* and lists them as follows:

Absolute: Perforation,
Pyloric stenosis,
Any possibility of malignancy, (in gastric ulcer)
Massive haemorrhage which does not stop in twenty-four hours.

Relative: Recurrence after adequate treatment.
Penetration into adjacent viscera.
Persistent oozing of blood and repeated gross haemorrhage.
Recurrence after palliative surgery.
All ulcers which fail to respond promptly to medical treatment.
Geographic, occupational and economic considerations. (Patients on relief cannot control adequate dietary precautions; men in mines and lumber camps are too far away as a rule to obtain medical treatment)

I would submit the thesis that we are not having proper respect for these indications, and would support it with a couple of case histories.

Case 1.

Miss R., twenty-five years old, school teacher, was referred to me in 1941 with the following history—For more than a year she had been suffering from abdominal distress and vomiting and had had a long history of dyspepsia. At the very earliest occurrence of symptoms they were controlled by the usual ulcer treatment, but eventually they failed to respond to any treatment and vomiting and loss weight persisted. She was sent to a hospital where X-ray indicated that there was dilatation of the stomach and considerable delay in emptying. In hospital she improved and was sent home in a short while. Within two months symptoms were as bad as ever and she was again sent to hospital. At this time the stomach was more grossly dilated and the retention much greater, some up to twenty-four hours. After a short while in hospital she was again allowed to go home to her long-suffering doctor, who for some time continued the medical treatment recommended.

In due course the inevitable recrudescence came, with increased loss of weight and vomiting of practically everything that entered the stomach. This persisted until she had gotten down to virtually skin and bone and to the point of not retaining water. At this point she was referred to me.

On admission she weighed less than seventy pounds, her nerves were shot, so that she hated for anyone to go near her. Even the giving of intravenous fluids was a nightmare for everyone concerned. She could take very little of food or water, and what she did take came back in large quantities, one or more times during each day. For weeks she was not an operative risk, but by means of transfusions, infusions and gastric lavage she was brought to the point where operation was considered reasonably safe. Her gastric acidity was about four times the highest normal. The stomach, which by our treatment had been reduced was still very large. About three-fifths of it was resected and a posterior Polya anastomosis done. That was nearly two years ago. Since then her weight has very nearly doubled, she is eating almost everything, is very happy and is again a useful member of her profession.

Case 2.

Is that of a man of fifty who was rushed to Halifax early one morning in a very serious state. Some five hours before, he had become seized with severe abdominal pain and vomiting. He was extremely emaciated, and the earlier history was that he had been under medical treatment for peptic ulcer for several years. His abdomen was tender and hard as a board throughout and the diagnosis of perforated ulcer was quickly made, but the fact that vomiting was present to a considerable degree was noted as a point of unusual interest. Before the anaesthetic was given he vomited two large kidney basins full. On opening the abdomen there was found free in the peritoneal cavity a large amount of the same kind of fluid that he had been vomiting. The source of this was soon found to be a large rent in the anterior wall of the prepyloric portion of the stomach, and a large amount of the same material was still contained within the grossly distended stomach. No opening into the duotenum from the stomach could be demonstrated. My impression was that the rent was caused by great pressure in a weakened part of the stomach, in a person emaeciated

from starvation. Further enquiry revealed that six months before, the symptoms had changed, pain and distress after food recurred more frequently and there was occasional vomiting of food which ordinarily had agreed. It was held that this was due to the medicine (Sippy tablets) not agreeing. That was changed again and again, but the symptoms persisted, vomiting increased and loss of weight and strength was progressive. Nothing but medical treatment had been suggested. He was in such bad shape that all that could be done was to suck out the abdominal cavity and the stomach, close the rent and institute continuous gastric drainage, until such time as he could stand some other procedure, and even that was too much. A similar case came under my care a few weeks later with results that were fatal within a few hours.

These cases, though extreme, are by no means isolated examples of the fact that we are not giving sufficient thought to the very real indications for surgical treatment and to the excellent results that accrue in properly selected cases.

With respect to the absolute indications, haemorrhage is quite a bone of contention. There are those who claim it is entirely a case for medical treatment and it is true that in most cases that is so. Of late there has been argument from many sources, that prompt operation for gross haemorrhage is better treatment. As in most things there is some truth in both positions. In younger subjects from middle age down medical treatment is very generally regarded as being the more satisfactory ,with a mortality rate so low as to be difficult for surgery to improve. Surgery should be reserved for the more persistent cases of this group. In the case of persons above middle life, where the mortality rate for medical treatment is so relatively high, surgical treatment must be accorded a higher place. What surgical treatment will be is to be decided in the individual case. It may be resection, or if the subject is not so robust then exposure of the ulcer by trans-gastric or trans-duodenal route, suture of bleeding vessel and gastro-enterostomy, may be the choice. Recurrent cases should be considered seriously as cases for surgery, even though they have improved under conservative management for the time is likely to come when they will not be as good a risk.

Obstruction: There are few who would not accept this as an absolute indication for surgery yet there is one place in which we have been misled. In the more active type of lesion, the treatment that is given preliminary to operation—the gastric lavage and strict diet—produces alleviation of the symptoms by reductions of oedema and spasm about the lesion.

In many cases the patient is likely to say, "I am so much better now, I shall defer the operation," and we being a very agreeable lot and anxious not to do unnecessary surgery, readily acquiesce. If the lesion is on the stomach side of the pyloris we should not acquiesce at all. If it is on the duodenal side acquiexcence should be qualified, so that at the first recurrence of distorted gastric function, surgery shall be proceeded with. If the lesion is a quite chronic one, then so much is scar that little or no hope may be entertained for prolonged freedom from symptoms and operation should be advised on the finding of even moderate retention. The results justify the procedure.

As to the type of operation we are going more and more to partial gastrectomy with some Polya type of anastomoses. It is true that every once in a while gastro-enterostomy gives a perfectly satisfactory result—indeed, I shall tell you of my most recent, where for a time at least the joke was on me. Three

months ago a man age 38 was referred to me for investigation and treatment. All signs and symptoms pointed to cancer of the stomach with partial obstruction. Operation was advised and refused. He wanted to go home. Some weeks later he came back asking for the operation. Obstruction and loss of weight were further advanced. He was prepared for resection, but when the abdomen was opened, the mass in the stomach was so great that resection was regarded as impossible. The mass was found to occupy more than half of the anterior wall of the stomach and to have gone around the greater curvature and infiltrated through the whole diameter on the posterior wall with gross attachment to the pancreas. Even gastro-enterostomy was unsatisfactory, since a proper placing was impossible, and indeed, the amount of available stomach wall anywhere was scarcely adequate. It was necessary to do a high anterior antecolic anastomosis. It was all we could do to relieve his obstruction, which now was about complete.

There were small areas of infiltration about the main mass and a number of firm lymph nodes in both omenta, one of which was removed. It proved to be inflammatory. We asked for him to return in three months. He got back in four bringing with him nearly thirty pounds more than he took from the hospital, with haemoglobin practically normal, *with a good appetite and no dietetic restrictions.* X-ray then showed some irregularity of the lower one-third of the stomach and a slowly functioning stoma of the gastro-enterostomy. There was no occult blood. In a further seven months, however, he was dead of carcinoma of the stomach.

That was a case, in which, even a badly placed gastro-enterostomy gave an excellent functional result; but while it must be admitted that they are sometimes good, there are many times when even the best gastro-enterostomy will not give good function and though it may at first, fails to do so later. There is no doubt that gastric resection offers a great deal more, and where conditions surrounding the operation are calculated to produce a low mortality rate, it is the operation of choice for a considerable number of surgeons, and that number is very much on the increase. It was not so long ago that an argument against it was that persons who had had a gastric resection were not able to tolerate great physical strain afterwards. Nothing is further from the truth; for some of my cases have been among hard-working men and they give results equal to or better than those of the so-called white-collar class. My earliest case in Halifax was and is a stevedore and he has been symptom free for nearly fifteen years with about half of his stomach, and that without dietetic restrictions. However, there are still enough protagonists of the gastro-enterostomy school to justify my making the following statement: (It is possible to quote from authorities of very radical views upon the subject but as my endeavour is to keep my own view reasonably conservative, I shall quote from Walters of the Mayo Clinic, who says):

"The advantages of gastric resection (partial gastrectomy) with a Polya anastomosis over gastro-enterostomy in the treatment of duodenal ulcer are the reduction of the quantity of gastric secretion and the development of a relative achlohydria in approximately seventy-five per cent of cases in which the Polya type of operation is performed. This contrasts with the development of relative achlorhydria in approximately ten per cent of cases in which gastro-enterostomy is performed." And it may be added, quoting from the same source, that this reduces the incidence of recurring ulcer fifty per cent more.

This understanding as to the type of operation constitutes a definite advance in our therapy. It is probable, however, that that which obtains in the field of pre-operative and post-operative care is greater still. The part which re-hydration plays in these as in many another kind of operative case is well known, but none the less constitutes a great advance, and the realization that the average human body can handle only about 8 grammes of sodium choloride, and 100 grammes of glucose a day, without producing undesirable results is its finishing touch. When to this we add the knowledge that the serum protein in these patients is frequently quite low, and we apply that knowledge and raise the protein to the normal level, we do a great deal to make the patient safe for surgery, and at the same time take a very real step toward the encompassing of our own peace of mind. For low serum protein means oedema around our anastomosis—whatever kind we employ—and oedema means the worry of a non-functioning or late-functioning stoma.

Perforation is our final absolute indication. Under this head there is only to repeat what is now almost an axiom: prompt operation and simple closure gives generally satisfactory results. Nor is it necessary when operation is prompt to fill the abdominal cavity with the sulphonamides. To insufflate a little into the edges of the abdominal wound, however, is not bad practice.

Some admittedly bad pictures have here been presented. They prove that we do not always observe these absolute indications. But, let us dismiss them if you like by saying that those cases are exceptional, and that in the main we admit, as medical men, that these indications are indeed absolute; what about the relative indications? Here, I am sure is where we shall find our points of greatest difference.

Recurrence after medical treatment: How often shall we repeat that treatment or how many recrudescences shall we allow before giving other advice? Or looking at the others again:

Penetration into adjacent viscers,

Persistent oozing of blood and repeated gross haemorrhage,

All ulcers which fail to respond to medical treatment,

Geographic, occupational and economic considerations,

How far do we go in the direction of accepting them as indications for surgery?

One final phase of this subject and I shall have done. It is suggested by one of the indications listed above: Ulcers which fail to respond to medical treatment. Gentlemen, there is no greater ally of ours in this work than the roentgenologist, but no matter how friendly you may be with him, don't let him assume the mantle of infallibility, or better still, don't act as if you expected him to be infallible, for he makes mistakes, gentlemen, the same as do we ordinary mortals.

We have already mentioned the importance of this in the differentiation of gastric cancer from gastric ulcer. Let me now present a case from the duoduodenum: W. S. Age 70, father of one of our graduate nurses, was referred to me in October 1941. He had the ordinzry symptoms of duodenal ulcer, but pain felt through to the back was more than usually a prominent symptom. The history showed that seven years before, he had undergone treatment for a duodenal ulcer, but that in the interim he had been well. X-ray examination

suggested that the old ulcer had been reactivated, or that a new one had occurred on the posterior wall of the duodenum. He went into hospital under strict conservative treatment, but after ten days his symptoms had not abated whereupon I questioned the diagnosis, discussed the matter with the patient and with his daughter and advised operation. A day or two later I opened the abdomen to find no peptic ulcer anywhere, but a carcinoma of the head of the pancreas, with only moderate dilatation of the gall-bladder. There was no jaundice. (Incidentally, with the cholecyst-gastrostomy which I then gave him he carried on at his trade as a plasterer for eighteen months, then, showing the progressive effects of pancreatic insufficiency, and of portal obstruction, he failed in strength and died, twenty-five months after operation.)

A more recent one is that of a man in whom the symptoms were, also, misleading. He had had several recent X-ray examinations before I saw him and I made the mistake of accepting their findings. Those examinations had indicated gall-stones but *nothing was found at X-ray in either stomach or duodenum.* At operation no gall-stones were found in the apparently normal gall-bladder, but, high on the posterior wall of the stomach, necessitating a resection of 3/5 of that organ, was an ulcer, the indurated area of which was $2\frac{1}{2}''$ in diameter and the crater so broad as to admit the end of the index finger.

Yes, the X-ray makes mistakes, probably, of course, no more than we do; indeed it is a wonder that from its world of shadows it contrives to be as accurate as it is. But "diagnosis is difficult" applies equally to it, and accuracy depends more upon the roentegenologist than upon the machine; indeed, I doubt if there is any department of medicine in which the training and experience of the man is so important as in X-ray diagnosis in gastro-enterology. In fine, it is a specialty of the highest order limited by the known potentialities of the apparatus and definitely proportionately qualified by the experience of the man who controls it. He is then a consultant, giving opinions which either may be very valuable or which, because of the limitations of either the machine of the man, may have to be disregarded, because the findings are not in keeping with clinical fact. My purpose in bringing this in is not so much to enhance the prestige of the roentgenologist nor yet to damn those totally unqualified in X-ray diagnosis but rather that I might accentuate the place of the clinician in our scheme of things. It is so easy to send the patient to the X-ray and accept without question and without further thought its positive or negative findings. Yet it is clearly the clinician's place to stand between the patient on the one hand and the X-ray and laboratory on the other, to correlate such facts and to accept or reject such opinions as may come to him. This is a duty which he must assume because only he can properly discharge it, and it is his prerogative, the exercise of which will bring benefit to his patient and satisfaction to himself as he finds clinical justification for his critical thought.

Blood Regeneration in Blood Donors

C. B. Weld, M.D. and M. E. B. Gosse, M.D.

IN these days when so many people are giving regular blood donations, the question of regeneration of blood may well be reviewed. Experiments with animals go far to explain the factors concerned but the exact time relationships in humans can only be found by clinical experience. In the Canadian Red Cross clinics it is customary to take 300 cc.-450 cc. blood, depending largely on the size of the donor. Experiences with animals in which much larger proportional amounts are usually taken are therefore not comparable.

Ebert, Stead and Gibson[1] have reported interesting studies with a series of professional donors with respect to the rate of volume restoration. They found that even after the withdrawal of 1000cc. amounts, (sufficient to cause circulatory collapse in nealy all donors) full volume was restored in 72 hours. Not for two hours was there any appreciable change in hemoglobin or plasma protein, then for the next four hours a small degree of blood dilution by protein free fluid was shown, after which normal volume and plasma protein were restored simultaneously within the next two or three days. Alstead[5] reports that this may take a week or more. Following a transfusion, therefore, the hemoglobin should begin to fall within a few hours but not reach its lowest level for at least two days. Thus it is clear that plasma volume and plasma protein restoration is so rapid as not to be a factor in determining the proper interval between blood donations. This is further indicated by a recent report by Co Tui et al.[2] These workers took 12 full donations at weekly intervals from one group of men and 8 donations at 2 day intervals from another group. They separated the cells from the plasma and reinjected the cells into the donor. There were no ill effects and no anemia. From an academic point of view this is an interesting development but the procedure would seem to be impractical in such a large scale effort as the Red Cross Blood Donor Service.

The formation of new erythrocytes and hemoglobin is however slower and becomes the limiting factor in donation frequency. Within a day or two of a donation there is a definite reticulocyte response; counts of about 10% retics showing increased hematopoeisis are reported by Martin and Myers[3]. Barer and Fowler[4] doing careful hemoglobin determinations, report that the original hemoglobin levels of the majority of their donors are restored in 7 weeks, that three quarters of their donors are fully recovered in 8 weeks, but that one quarter may take as long as 15 weeks. Iron administration shortened the recovery period of the average donor to 5 weeks but the effect is transient and even with continuous administration the effectiveness is lost after 2 or at the most 3 donation periods. Alstead[5] also found an 8 week interval to be satisfactory. On the other hand Martin and Myer[3] and Brewer[6] suggest a three month interval. They however indicate that this allows an ample margin of safety and it should be pointed out that their donations on the average are considerably larger than in the Canadian Red Cross clinics. Against these findings however, several groups of workers (7,8,9,) report that with professional donors multiple donations may be given at much more frequent intervals with no harm to the donors and with no anemia.

The standard donation interval in the Canadian clinics is 10 weeks. In the Halifax clinic donors are not recalled in less than this time though they are accepted freely if they come in voluntarily in 8 weeks. Occasionally men are

accepted in 6 weeks but never repeatedly at this interval and not at a shorter time.

Nearly all the work reported above has been done with male donors and all the workers report that with women blood formation is slower and anemia more apt to develop. Few concrete figures are given however.

The Halifax clinic was one of the earlier Canadian clinics to accept women donors freely and beyond the general reports that women were more apt to develop anemia than men, there was no backlog of experience with large groups of women giving repeated donations to use as a guide to routine measures of control. At that time regular or routine hemoglobin determinations were not considered necessary by other large Canadian clinics and the matter was left entirely to our own discretion. Early in the days of the Halifax clinic the need of regular hemoglobin measurements in women donors became apparent and the present routine has been gradually evolved.

In the case of men, we have found hemoglobins of 90%-100% so consistently, even after several donations, that we have not in the past considered it necessary to do the test as a routine. It is of course done whenever there is any sign or suggestion from the patient of the need of or desire for a test; only in a very few instances have we encountered an important fall. Even those few men who report that since their last donation they have felt tired and who claim that their friends say they look pale, seldom show a fall in hemoglobin. After 8-12 donations at intervals of 8-10 weeks a number of men will show a hemoglobin of 80%-90% usually without any symptoms. Some will show a lower figure and it is well to check the hemoglobin of men from time to time after 5 or 6 donations. On the other hand, with the instrument (Newcomer[11]) we are using, nearly all the women who come as donors for the first time have hemoglobins in the 70%-89% range, averaging about 80%. Most of these, even if they start off with a hemoglobin in the seventies, give several donations without any appreciable alteration of their level and without any subjective symptoms of blood loss. A number however do show a sharp fall in hemoglobin, gradual in some cases and abrupt in others, which may occur after one or not until after several donations. Our practice is to do the hemoglobin on each woman donor before she gives blood. If it is below 70% she is not accepted. It is checked every time she comes in if it is below 80%, but only at every second or third visit if it is above this figure. If her hemoglobin is in the low seventies or is dropping, she is given iron and the amount of blood taken is often reduced. If she doesn't respond promptly to iron medication or if there is any reason to suppose that she has a real anemia due to some other cause, she is referred to her own physicians because of peculiar symptoms or complaints they may describe; no medical advice apart from that directly pertaining to blood donations is given in the clinic.

The iron given is Ferrous Sulphate, gr. 3, 1 tablet t.i.d.p.c. This has been our practice for about two years but only very recently has the national donor committee accepted our lead. They are now purchasing 5 grain tablets centrally and distributing them to the various clinics over Canada. When our present stock of 3 grain tablets is exhausted we will use the larger tablets.

The impression gained from our group of several thousand donors, many of whom have given many donations, is that they differ widely in their individual hemoglobin regeneration rate. This is possibly related to nutritional factors; one would not expect malnutrition in our group of donors, but individual deficiencies are not impossible. Snapper et al[10]. have reported a large incidence of anemia in Chinese donors and these workers suggested general undernutrition

as the cause. If the donation rate is less than the regeneration rate, an indefinite number of donations may be given; this applies to most men giving 400cc. every 10 weeks. If the donation rate is only slightly in excess, several donations may be given before a noticeable fall in hemoglobin results; this is possibly the status of a few men and of many women. When a donor who has given many times without ill eflects, does show a little reduction in hemoglobin it is well to consider the possibility that the regeneration rate has been slightly exceeded and is finally becoming apparent. Such a donor may be given iron or be advised to skip one donation period. If the donation rate considerably exceeds the regeneration rate, anemia will become apparent after only one or two donations and in these the donation frequency is sharply reduced and the regeneration rate is stimulated by iron in order to allow them to continue as donors; a number of women fall in this category.

Using the precautions described above we feel that the donors are well safeguarded. It would of course be nice to have a hemoglobin record of every donor every time but as the extra work is considerable and as many donors object to the pricking of the finger and the delay it entails, it has not been considered necessary.

REFERENCES

1. Ebert, Stead and Gibson, Arch. Int. Med. 1941, 68, 578
2. Co Tui et al. J. Am. Med. Ass. 1944, 124, 331.
3. Martin and Myers. J. Lab. & Clin. Med. 1935, 20, 593.
4. Barer and Fowler. J. Am. Ass. 1942, 118, 421. Am. J. Med. Sc.. 1943, 205, 9.
5. Alstead. Lancet, 1943, 1, 424.
6. Brewer. Br. Med. J. 1939, 1, 895
7. Griffin and Haines. J. Am. Med. Ass. 1923, 81, 532.
8. Jones, Widing and Nelson. J. Am. Med. Ass. 1931, 96, 1297.
9. Brinck and Oetinger. Med. Klin. 1937,. 33, 307.
10. Snapper et al. Chinese Med. J. 1939, 56, 403.
11. Newcomer. J. Biol. Chem. 1919, 37, 465.

Obituary

THE death occurred suddenly at his home at Whitney Pier on April 9th of Dr. William Ross McRae at the age of seventy. He had returned from a professional call and had been in the house a few minutes when he was stricken. Death came before aid reached him and was due to a heart attack. Dr. McRae was born at Baddeck, a son of the late Mr. and Mrs. John McRae. He received his early education there and later went to Dalhousie University where he graduated in Arts in 1894. From Dalhousie he proceeded to McGill University and in 1897 received his medical degree. A classmate was the late Dr. J. J. Roy of Sydney who died in May, 1942. For several years Dr. McRae practised in Baddeck and in 1900 went to Sydney with the advent of the opening of the steel plant and resided in Whitney Pier since then. In addition to his private practice he was also on the staff of the Dosco Emergency Hospital. He was a member of St. Andrew's Masonic Lodge, a member of Trinity United Church, the Cape Breton Medical Society, the Medical Society of Nova Scotia, and the Canadian Medical Association. Quiet and unassuming, Dr. McRae was beloved by all, as his qualities as a physician and citizen, plus his acts of kindness and charity endeared him to everyone.

His wife died in 1917 and he is survived by one daughter, Mrs. Henry Williams, the former Isabel McRae, whose husband, Dr. Williams of Montreal, is overseas with the Canadian Army Medical Corps. A grandson also survives and one brother, John McRae, retired mariner living in Staten Island, N. Y.

The funeral was held on the 11th, with service at the house and burial at Baddeck.

"In Appreciation"

The untimely passing into eternity of Dr. William McRae of Sydney has occasioned much sorrow and deep regret not only throughout the Province of Nova Scotia but especially in Sydney and its surrounding communities amongst those whom he served so well for many years.

One cannot help but look back in retrospect upon the life of Dr. MacRae —a representative of a type of physician that is rapidly disappearing from the scene. A native of Baddeck, N. S., and a graduate of McGill University, Dr. MacRae practised medicine in Sydney for over forty years. His name was a household word to adult and child alike—in view of his clinical skill, untiring devotion and tolerance to his patients. Above all, he paid very little attention to the materialistic side—and with him the rich and the indigent occupied an equal plane. He exemplified the cardinal precepts of a noble profession. Of his many attributes, modesty, kindness of heart, sincerity and humanitarianism stand out to an accentuated degree. He did not strive for riches or fame but patiently plodded the daily routine of administering to the ill and alleviating suffering. It is therefore not surprising that he occupied a position of affection coupled with dignity among patients and also with his medical colleagues and nursing sisters. There will be countless thousands of various races and creeds, many of whom he brought into this world, who will cherish his memory in a spirit of grateful appreciation—and particularly the people of the Whitney Pier district of Sydney where he resided for so many years and to whom he was such a familiar figure. What greater monument could one erect in a life time than the ever enduring esteem and affection that was established after so many years of ministering to the ill?

It is therefore in a spirit of sincere appreciation that the writer pens these few words eulogizing the life of a "beloved physician"—truly a befitting caption —whose memory will always be enshrined in the hearts and minds of those to whom he cared for and to his friends. For in the memorable words of Osler, "To have striven, to have made an effort, to have been true to certain ideals, this alone is worth the struggle."

E. David Sherman, Capt. R.C.A.M.C.