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BLEEDING AFTER PERFUSION FOR OPEN HEART SURGERY IMPORTANCE OF UNNEUTRALIZED HEPARIN AND ITS PROPER CORRECTION

BY

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The use of extracorporeal circulations for open cardiac surgery has presented many new and unique problems. One of these is a disturbance of blood-clotting due to passage of the blood through the circuit of the pump and oxygenator. A haemorrhagic state may follow perfusion of a patient. It has been attributed to a deficiency of one or other of the coagulation elements in the blood, and these are discussed later.

One additional factor which can contribute to the haemorrhagic state is the presence of unneutralized heparin after perfusion. The detection and elimination of this is important and is the subject of this paper.

An anticoagulant is essential in extracorporeal circulations to maintain the fluidity of the blood and to protect the platelets and plasma-coagulation factors in the pump-oxygenator circuit. It must be potent, non-toxic, rapid in action, and be quickly and easily neutralized. Heparin best fulfils the requirements, and is the anticoagulant used for this type of surgery. The drug (2 mg./kg.) is given to the patient immediately before perfusion with heparinized donor blood (20 mg./500 ml.) from the pump-oxygenator.

For haemostasis at the end of the perfusion the circulating anticoagulant is neutralized by an anti-heparin drug—commonly protamine sulphate. To ensure that this has been done adequately we have used a rapid and sensitive test for the detection of traces of heparin. This is the thrombin clotting-time of plasma, and it is described below. We have found by using this test that traces of heparin may remain in the blood-stream after protamine administration and be enough to prolong the oozing state post-operatively both in the experimental animal and in patients. "Oozing" is an apt description of this state with its slow, steady loss of blood necessitating careful haemostasis. The operation time is prolonged, further transfusion is required, and post-operative drainage is considerable. Haematomas may form in the wound and in the chest. In the early experimental work on dogs a number succumbed because of excessive bleeding before it was realized that the complete elimination of heparin was so important. Since following this policy we have had no serious bleeding after perfusion.

Blood Tests for Heparin

Heparin is believed to affect all stages of blood coagulation. It is generally thought that the characteristic action of heparin is a reversible interference with the clotting factors rather than a permanent inactivation (Jaques, 1943; Forwell and Ingram, 1956). It interferes with the generation of thromboplastins preventing the

activation of prothrombin (Fischer, 1935; Overman, 1949), inhibits the conversion of prothrombin to thrombin (Howell, 1917; Brinkhous *et al.*, 1939), and prevents the action of thrombin on fibrinogen (Mellanby, 1934; Quick, 1938).

Tests involving one or more of the stages of blood-clotting have been used in the detection and estimation of heparin after perfusion. The whole-blood clotting-time (Lee and White, 1913) represents a complex series of reactions with a poor end-point which is influenced by many intrinsic and extrinsic variables. It is a poor indicator of the state of coagulation *in vivo*. Many accelerating artifacts may cause a normal value to be obtained despite the presence of heparin.

Protamine titrations (Allen *et al.*, 1949; Perkins *et al.*, 1956; Hurt *et al.*, 1956) which depend on the whole-blood clotting-time are open to the same sources of error and are therefore not a true measure of heparin activity. The determination of the total circulating heparin in the patient after perfusion involves a necessarily approximate estimation of the blood volume, which adds to the inaccuracies when the original errors in the titration are multiplied by the estimated blood volume. They can give a wide range of error in the estimation of the total heparin which requires neutralization after perfusion.

The one-stage prothrombin time (Quick *et al.*, 1935) is more rapid than the whole-blood clotting-time, has a good end-point, and is less influenced by artifacts. For these reasons LeRoy *et al.* (1950) used a modification of it as the indicator instead of the whole-blood clotting-time in estimating heparin activity by a protamine titration. However, the final two stages of coagulation are involved and the test is therefore influenced by more factors than is the thrombin clotting-time. For the required degree of sensitivity to heparin we have found it more convenient to adjust the thrombin clotting-time than the prothrombin time to our needs, and this is discussed further below.

The thrombin clotting-time measures fibrin formation, which is the final stage of coagulation:

It is one of the simplest of all clotting tests and has a low experimental error (Ingram and Armitage, 1952; Armitage and Ingram, 1958). A variation of it has been used by Blombaek *et al.* (1955) in a method of estimating heparin after perfusion.

The main factors affecting the reaction, apart from heparin, are the thrombin and fibrinogen concentrations. The test is made a suitably sensitive indicator of heparin activity by adjusting the thrombin concentration to give an appropriate control clotting-time. We have considered the influence of fibrinogen and heparin concentrations on our thrombin clotting test and also the effect of changes in the pH of the blood. The latter effect was investigated by Burstein and Guinand (1954), and from their work it appears that the pH range that might be encountered after perfusion would not influence the test. The fibrinogen concentration, as is described below, does not usually in practice enter a range which affects the test, so that after perfusion heparin is the chief factor influencing the thrombin clotting-time.

Method of Performing the Thrombin Clotting Test

The test is performed by adding a thrombin and calcium chloride solution to citrated platelet-poor plasma and timing the clot formation. Ionized calcium is added to the test system as it affects the thrombin-fibrinogen reaction (Ingram, 1955).

Each blood sample (4.5 ml.) is mixed with 3.8% sodium citrate (0.5 ml.), giving a ratio of 9:1. The sample is then spun for 5 to 10 minutes at 3,000 r.p.m. and the citrated platelet-poor plasma removed.

Calcium-thrombin solution is prepared, using small quantities of reagents. A few granules of dry thrombin topical (Parke, Davis & Co.) are dissolved in a mixture of equal quantities of normal saline (0.9%) and M/40 (280 mg./100 ml.) calcium chloride (total about 6-8 ml.).

Pre-operative plasma 0.1 ml., prepared as above, is placed in a glass tube (7 by 65 mm.) in a water-bath at 37° C. Into this is rapidly blown 0.2 ml. of the calcium-thrombin solution and a stop-watch started simultaneously. The tube is transilluminated and gently shaken in the water-bath until a fibrin clot forms. This is indicated by a preliminary clouding of the plasma followed by cessation of its movement. The latter is taken as the end-point. The tube should not be shaken vigorously, as the early formation of the delicate fibrin network can be broken up, delaying the end-point.

The clotting-time is adjusted to 10-12 seconds either by further dilution of the calcium-thrombin solution with equal quantities of saline and M/40 calcium chloride or, alternatively, by adding more thrombin granules. The mean of two or three replicate readings is usually taken, and this clotting-time of pre-operative plasma acts as the control.

The mean of the thrombin clotting-times of samples of plasma after the heparin antidote has been given is determined with this calcium-thrombin solution. It is compared with the clotting-time of the sample obtained pre-operatively, which is checked again on each occasion, as it may become slightly prolonged with the passage of time.

As stated above, this thrombin clotting-time may be altered by two main factors—a change in fibrinogen concentration or the presence of heparin—and these are now considered.

Effect of Fibrinogen on Thrombin Clotting-time

After perfusion there is usually a fall in the fibrinogen content in the patient's plasma of about

75-100 mg./100 ml. of plasma—that is, a reduction of about 20-30%. It is important to determine what effect decreased fibrinogen concentration might have on the thrombin clotting-time.

Pooled platelet-poor plasma from several normal fasting humans (pre-operative patients) was prepared and a quantity of it defibrinated by the addition of small quantities of thrombin. The untreated pooled plasma was then serially diluted with the defibrinated plasma to give decreasing percentages of fibrinogen. Duplicate readings of the thrombin clotting-time were then obtained for each dilution. The effect of the reduction in the fibrinogen concentration on the thrombin clotting-time is shown in Fig. 1.

FIG. 1.—Effect of the reduction in fibrinogen concentration on the thrombin clotting-time. 0% reduction is equivalent to 300 mg. of fibrinogen per 100 ml. of plasma.

This indicates that a reduction of more than 50% of the fibrinogen may occur before there is an appreciable prolongation of the thrombin clotting-time. This reduction is about twice that usually found in patients after perfusion, so that any increase that may be found in the thrombin clotting-time must indicate the presence of heparin.

Effect of Heparin on Thrombin Clotting-time

Heparin is known to inhibit the action of thrombin and so delay fibrin formation. The effect of various concentrations of this drug on the thrombin clotting-time was determined. The effect on the one-stage prothrombin time (Quick) was also determined, and the two were compared in order to assess the relative usefulness of the two tests in the detection of unneutralized heparin in perfusion cases.

Part of the same pooled plasma from normal humans, described above, was heparinized (0.1 mg./ml.), then diluted with the non-heparinized pooled plasma to give decreasing concentrations of heparin. The average thrombin clotting-time and the average one-stage prothrombin time of duplicate readings were determined for each concentration of heparin within 30 minutes of preparing the plasma samples (Fig. 2).

FIG. 2.—Effect of different heparin concentrations on the thrombin clotting-time (TH.CL.T.) ●—●, and on the one-stage prothrombin time (PR.T.) ○—○, when performed by the techniques described.

This shows that with the techniques we have used the thrombin clotting-test was more sensitive to very low concentrations of heparin (4–8 $\mu\text{g./ml.}$) than the one-stage prothrombin test (20–40 $\mu\text{g./ml.}$). Concentrations of 5–10 $\mu\text{g.}$ of heparin per ml. of plasma are approximately equivalent to those which may be found in post-perfusion plasmas after protamine administration and which may cause or aggravate bleeding.

The thrombin clotting-time of such plasmas is therefore much more influenced by heparin than by the lowered concentrations of fibrinogen (Fig. 1) that are usually found after perfusion (Gollub *et al.*, 1959).

A prolongation of the thrombin clotting-time of the plasma taken after the administration of the antiheparin agent compared with that of the pre-perfusion plasma is thus more likely to be due to the presence of unneutralized heparin than to a lowered fibrinogen concentration.

This can be confirmed by adding toluidine blue to the thrombin-clotting-reaction system. This was found to be better than using protamine, which has itself a markedly accelerating effect on the thrombin clotting-time that might mask the retarding effect of traces of heparin.

Toluidine-Blue-Thrombin Clotting-time

Toluidine blue is a specific antiheparin (Holmgren and Wilander, 1937) and will return a prolongation of the thrombin clotting-time due to heparin to that of a pre-operative control (Biggs and Macfarlane, 1957), and may therefore be used as a qualitative test for heparin. The toxicity of this dye precludes its use *in vivo*. Experiments were made to find the best concentration and quantity of toluidine blue necessary to neutralize traces of heparin *in vitro*. The accelerating effect of toluidine blue on the thrombin clotting-time and the ease of visualization of the end-point must be considered (Fig. 3).

FIG. 3.—Effect of (a) the colour of toluidine blue on the determination of the end-point (above) and (b) different concentrations of it on the thrombin clotting-time (below), using 0.05 and 0.1 ml. of each concentration. Toluidine blue solution 0.05 ml. of concentration 0.5 mg./ml. does not interfere with either.

FIG. 4.—This shows that the volume and concentration of toluidine blue chosen for the test (0.05 ml. of 0.5 mg./ml.) is sufficient to neutralize heparin in concentrations up to 20 to 30 $\mu\text{g./ml.}$

Thus 0.05 ml. of 1 in 2,000 (0.5 mg./ml.) solution of the dye in normal saline was found suitable. This is added to the plasma prior to the addition of the calcium-thrombin, and it prolongs the normal thrombin clotting-time by 2 to 4 seconds (see Fig. 5). This concentration and volume of the dye neutralized approximately 20–30 $\mu\text{g.}$ of heparin

per ml. *in vitro* (Fig. 4) and is adequate for post-perfusion traces. If more toluidine blue is needed 0.1 ml. of the 1 in 2,000 solution can be used, but the end-point is more difficult to see because of the colour, especially in the presence of haemolysis. This strength of toluidine blue is easily prepared from a stock 1 in 100 solution.

Perfusion Cases

The following routine was adopted after perfusion in experimental studies using dogs and in patients undergoing surgery. The thrombin clotting-time was determined on the pre-operative plasma and compared with that of the plasma taken 10 to 15 minutes after administration of the heparin antidote. If the thrombin clotting-time of the latter was prolonged then toluidine blue was added to the test systems of both plasmas. If the clotting-times were then within a few tenths of a second of each other, it confirmed that the prolongation was due to the presence of traces of unneutralized heparin and not to any decrease in fibrinogen concentration.

A further dose of the heparin antidote would then be administered, especially if there was troublesome oozing from the wounds. The tests were repeated 10 to 15 minutes after this dose. The dosage scheme that we have found most suitable is given in more detail below.

Three examples of the use of the tests are given in Fig. 5. All show the presence of heparin after protamine administration and all had a troublesome bleeding after perfusion.

The first patient studied (Fig. 5 A) had a normal whole-blood clotting-time (Lee and White) after operation, despite the abnormal bleeding and the presence of heparin. The control thrombin clotting-

FIG. 5.—Three perfusion cases illustrating the use of the tests described in the detection of traces of heparin causing bleeding after perfusion. V.S.D.—Ventricular septal defect. A.S.D.—Atrial septal defect.

times on the pre-operative plasma without and with toluidine blue are shown. After the administration of 2 mg. of protamine for every 1 mg. of the heparinizing dose given to the patient (referred to as a ratio of 2:1), the thrombin clotting-time of the plasma without toluidine blue was prolonged. The addition of toluidine blue returned the time to that of the control test. This confirmed that heparin was still present in the patient and caused the oozing, as no other marked defect of the major clotting elements was found. The oozing in this patient was controlled surgically and further protamine was not given.

The results of the first tests that were done on a second patient after administration of protamine (Fig. 5 B) showed that more protamine was required, and a total of 3 mg. for every 1 mg. of the heparinizing dose of the patient was given (a ratio of 3:1). As will be seen, this was not sufficient to eliminate all the heparin, and no other clotting defect was noted. The oozing was most troublesome and prolonged, and the post-operative drainage was marked. Further protamine was not given because of the theoretical danger of the anticoagulant effect of this drug. However, we have since given totals of 4:1 (8 mg./kg.) in experimental animals without ill-effect.

The third example (Fig. 5 C) showed satisfactory elimination of heparin and control of the bleeding state with further protamine to a total of 3:1.

The tests can be rapidly performed immediately after perfusion and after the initial dose of heparin antidote, and answers can be given before the chest is to be closed and before the levels of other clotting factors in the blood are estimated. Residual heparin can be quickly detected and then eliminated as a cause of bleeding after perfusion.

As a result of our experience with these tests in experimental and clinical perfusion cases, we have found the following dosage schemes of heparin antidotes to be satisfactory where a heparinizing dose of 2 mg./kg. had been given to the patient. When we used protamine sulphate the best routine was to give a dose of 4 mg./kg. (a ratio of 2:1) initially and then further doses of 2 mg./kg. (1:1 ratio) if the tests indicated the persistence of unneutralized heparin.

For reasons which we mention below, we have changed to the use of a new heparin antidote, hexadimethrine bromide ("polybrene") instead of protamine. The routine found to be best with this was to give 2 mg./kg. (1:1) initially and then a further dose of 1 mg./kg. (0.5:1) if the tests showed the persistence of unneutralized heparin.

The dose of heparin antidote is at present conveniently based on the heparinizing dose given to the patient and is thus related to body-weight. However, factors affecting the total circulating heparin in the patient during perfusion should also be considered in the determination of antiheparin requirements, and this is discussed below.

Discussion

The disturbances of clotting elements induced by blood traversing an extracorporeal circulation, and the causation of the bleeding state which may follow, have occupied the attention of many workers using artificial heart-lung machines for open cardiac surgery.

A reduction in the quantity and possibly also quality of the platelets, and of all the plasma coagulation factors, occurs during perfusion, and a deficiency of one or more of these clotting elements has been implicated as the cause of bleeding (Allen, 1958; Gollub *et al.*, 1959). Other possible causes have been suggested. Osborn *et al.* (1955), Allen (1958), and von Kaulla and Swan (1958) found evidence of increased fibrinolytic activity. Release of thromboplastins with consumption of essential clotting factors was postulated by Osborn *et al.* (1955) and by Brown and Smith (1958). A new circulating anticoagulant was suggested as a cause by von Kaulla and Swan (1958).

There is thus no general agreement, among those who have studied alterations in the natural coagulation elements of the blood, on what may cause persistent bleeding after perfusion.

By adopting the tests described, we have found the detection and elimination of unneutralized heparin to be an important factor in reducing bleeding after perfusion as judged by improved experimental and clinical results.

Heparin interferes with haemostasis by preventing the cohesion of platelets (Murray *et al.*, 1937; Roskam, 1954; Hugues, 1954), and by inhibiting the formation of a fibrin clot. It can also cause abnormal bleeding if associated with other haemostatic defects which by themselves would be insufficient to produce haemorrhagic manifestations (Stefanini, 1953; Roskam, 1954; Craddock *et al.*, 1955). During perfusion there is frequently a gradual onset of oozing from the incised tissues. This occurs despite careful surgical haemostasis beforehand and proceeds in a slow but steady manner at a time when all efforts are concentrated on the open cardiac procedure. The fact that the oozing is first noted during perfusion and can be arrested afterwards by heparin antidote makes it likely that it is due to the action of heparin.

Complete neutralization is therefore essential and adequate quantities of heparin antidote must be given. The effectiveness of this is checked by the thrombin clotting tests and the clinical results. Elimination of these traces of heparin has been found to control excessive bleeding, and other clotting tests can then be validly carried out. So far in our practice other clotting deficiencies have been insufficient to cause bleeding.

The correct requirements of protamine or polybrene are important, but are difficult to assess accurately. At present it is the usual practice to base the requirements on the heparinizing dose of the patient (2 mg./kg.) and express this as a ratio of milligrams of antidote per milligram of heparin. We have found considerable variation from 1½:1 (3 mg./kg.) up to 4:1 (8 mg./kg.) or more, in the total protamine needed for effective neutralization both in dogs and in patients after perfusion. With polybrene, however, the total requirements have been more consistent, and a ratio of 1:1 (2 mg./kg.) has been adequate in most cases.

Why should there be this variation in antidote requirements and uncertainty in the action of protamine? There are two possible reasons for it: (1) that there is a variable increase in anticoagulant during perfusion, and (2) that there is variation in the neutralizing effect of protamine.

The concentration of heparin in the patient's blood prior to perfusion (approximately 0.04 mg./ml. or 40 µg./ml. of plasma) is increased by the heparinized

donor blood (approximately 0.07 mg./ml. or 70 μ g./ml. of plasma) as they mix in the heart-lung machine and body. The volume of donor blood used during this time is about twice that of the blood volume of the patient. The resulting concentration of heparin is about 0.06 mg./ml. or 60 μ g./ml. of plasma, an increase of about half after perfusion over the heparinizing dose given to the patient. It has been our practice to keep the heparin concentrations to a minimum without losing the efficiency of its anticoagulation. We have found that 2 mg./kg. for the patient and 20 mg./500 ml. for the donor blood is satisfactory. With a dose of 1.5 mg./kg. and 15 mg./500 ml. gelatinous clots can form on storage of the donor blood and on the filters of the machine during perfusion.

This increased amount of heparin will be affected by the rate of elimination of the anticoagulant during the perfusion period. The exact modes and rate of elimination of heparin have not yet been fully established. Eiber and Danishefsky (1958) have studied its excretion by the kidneys and deactivation by the liver and other tissues. Jaques (1940) and Jaques and Ricker (1948) showed its destruction by a plasma factor, and van Creveld (1954) described an antiheparin factor in platelets.

The rate of elimination of heparin might be expected to vary from patient to patient, depending on the degree of disturbance of renal and hepatic function and of the natural antiheparin factors during perfusion.

For these reasons there will be a variable amount of heparin requiring neutralization in the patient at the end of perfusion. It might therefore be inaccurate to base the antidote requirements entirely on the initial heparinizing dose given to the patient and so relating it to body weight. The requirements should, in theory, be related to the quantities of heparin given to the patient directly and in the donor blood and also to the amount eliminated and possibly added by the patient during the perfusion, were it possible to determine these things.

In practice, however, we have found it rapid and convenient, at the end of the perfusion, to give an initial dose of the heparin antidote based on the body-weight of the patient. This dose in most cases is sufficient to deal with the heparin present after perfusion. If there is any unneutralized heparin left after this it is shown by our tests, and further doses given until the tests and clinical state show satisfactory elimination of the heparin. The dosage schemes we have adopted are given above.

Another factor to be considered is the effectiveness of the neutralizing action of protamine. It may vary slightly with the preparation used, but this is probably of less importance than other factors affecting its neutralizing activity. These factors are under further investigation and will be reported in greater detail elsewhere, but the following findings are important.

Protamine is known to combine with plasma proteins (Shelley *et al.*, 1942), especially fibrinogen (Mylon *et al.*, 1942). We also have found this to be so, and it is probable that competition for protamine occurs between the proteins and heparin, so reducing the effectiveness of the protamine.

Dissatisfaction with protamine in the initial clinical and experimental cases led us at an early stage to the investigation and use of the new antiheparin drug,

polybrene (F. Gerbode and J. J. Osborn, 1958, personal communication). This has proved to be more efficient than protamine in neutralizing heparin as judged by clinical results and laboratory tests, and will be the subject of a more detailed report. There appears to be no competition for polybrene between plasma proteins and heparin.

It is of interest to note that more protamine is needed to neutralize heparin weight for weight than is commonly recognized. We have found that at least 1.5 mg. of protamine is required for the complete neutralization of 1 mg. of heparin *in vitro* and *in vivo* in normal human subjects and unperfused dogs. This neutralizing dose was also found necessary by Leroy *et al.* (1950). It is more than the 1 mg. of protamine for each milligram of heparin that is usually recommended. Those who use a titration or assay method of estimating heparin after perfusion should therefore use the higher dosage of protamine to neutralize it in order to avoid leaving any residual heparin.

In our clinical and experimental practice the dosage schemes described and used in conjunction with our laboratory tests and clinical assessment have ensured the complete neutralization of heparin after perfusion. Post-perfusion bleeding caused or aggravated by traces of heparin has thus been eliminated.

Summary

The disturbance of coagulation factors resulting from the use of extracorporeal circulations sometimes leads to bleeding after perfusion. Incomplete neutralization of heparin at the end of perfusion has been found to be an important factor.

The thrombin clotting-time of plasma can conveniently be adjusted so that it is very sensitive to traces of heparin. It is little influenced by changes in fibrinogen concentration caused by perfusion, and may therefore be used to detect unneutralized heparin after perfusion. The addition of toluidine blue to the test system may be used as an additional test to confirm the presence of unneutralized heparin.

These tests have therefore been employed for the rapid detection of traces of heparin which may be left after administration of the heparin antidote at the end of perfusion.

Their routine application in the laboratory in perfused dogs and in clinical patients is described. Traces of unneutralized heparin have been a frequent finding, and its elimination has reduced post-operative bleeding.

A consequent increase in protamine dosage has followed, and totals varying from 2 to 4 mg. (4-8 mg./kg.) of protamine for every 1 mg. of the heparinizing dose of the patient have been used without side-effects.

The variation and uncertainty of heparin neutralization are discussed. They have led to dissatisfaction with protamine. The reasons for them are discussed.

Hexadimethrine bromide (polybrene) has been found to be more efficient and has replaced protamine in our practice. A satisfactory dosage scheme for both drugs is described.

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"Over 21,000 health centres for mothers and children receive assistance from U.N.I.C.E.F. (United Nations Children's Fund) and W.H.O. (World Health Organization). Their work and the health policies pursued jointly by the two international bodies were reviewed at a meeting held in Geneva from December 3 to 5. In the Eastern Mediterranean region, the main health problems in children with which the centres have to deal are malnutrition, diarrhoeal diseases, and respiratory and eye diseases. In Africa, also, malnutrition, particularly kwashiorkor, and malaria are very commonly seen. In the Americas the most common causes of disease and death in children are diarrhoea and respiratory infections, with nutritional disease as a probable third. These and other facts emerge from a detailed study by W.H.O. of selected mother and child health centres in all parts of the world." (W.H.O./54.)

CLINICAL AND METABOLIC STUDIES IN THYROID DISEASE*

BY

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In this lecture I shall first discuss the diagnosis and treatment of hypothyroidism. Though what I have to say will be concerned chiefly with the form which arises from primary disease of the gland, I shall also speak about post-therapy and pituitary types of hypothyroidism and about the clinical syndrome we call Hashimoto's disease. Finally, I propose to describe observations on certain changes in metabolism which take place in response to over- and under-activity of the thyroid gland.

Hypothyroidism arises from a diminution in the amount of circulating thyroid hormone and is usually the result of partial or complete destruction of the gland. I do not propose to use the terms myxoedema and hypothyroidism interchangeably. This is often done, but in my opinion myxoedema should be used to describe not a disease but a particular type of skin manifestation which occurs only in some cases of hypothyroidism. It is usually obvious in the severe forms of the disease but is rarely seen in mild cases or when hypothyroidism is secondary to hypopituitarism. When hypothyroidism is of moderate severity even experienced clinicians may differ when asked to say whether or not the physical sign myxoedema is present. The student should be taught, therefore, to recognize hypothyroidism when myxoedema is absent, and he is apt to be confused if the terms are regarded as interchangeable.

Until a few years ago the cause of the atrophy of the thyroid gland found in most cases of hypothyroidism was unknown, but there is now evidence that in many instances it may be produced through the agency of auto-immunizing mechanisms. In a small minority of cases of hypothyroidism the pituitary gland is the site of the primary lesion, but in these there is usually evidence of insufficiency of hormones other than thyrotrophic stimulating hormone (T.S.H.), and the full syndrome of panhypopituitarism (Simmonds's disease) can be distinguished clinically from primary hypothyroidism.

A common type of hypothyroidism seen in clinical practice is the result of overtreatment thyrotoxicosis. This condition is of special interest, since the date of onset of the disorder can be placed within fairly narrow limits. The development of the condition is relatively rapid, and many of the clinical features of hypothyroidism tend to be accentuated so that the clinical picture differs somewhat from that of primary disease of the gland.

Recently a small group of patients has been recognized in which a genetic defect in enzyme systems has led to the production of iodinated compounds resembling the thyroid hormones but without their metabolic effects (see Stanbury and McGirr, 1957). These patients always have enlarged thyroid glands and present as goitrous cretins, though it is possible that this mechanism may also account for a proportion of adult cases of so-called sporadic goitre (McGirr *et al.*, 1959).

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