hypertension, and the consensus was that the medical treatment of hypertension is successful in some cases but that those who do not respond to medical treatment should be considered for operation and that there are certain patients who benefit more from medical treatment after they have had surgical treatment. The treatment of hypertension today is still controversial, and one must keep an open mind as to the most efficacious methods of treatment. At present there seems to be no one treatment which is a solution to the problem. Salt-free, low-sodium and rice diets and new drugs, which have been or may be developed, may alter the progress of the disease, and I am sure that surgeons would not insist on operative measures if other treatments proved superior. I appreciate the discussion of Dr. de Takats, Dr. Poppen and Dr. Allen, but I would like to leave with you the idea that it behooves us all to maintain an open mind with regard to the treatment of hypertension. Some day it may not be necessary to operate for the relief of hypertension, as physiologists, internists and surgeons all agree that a physiologic mechanism is involved in the causation of hypertension which, if found, may clarify our problem.

INDICATIONS FOR REMOVAL OF NONTOXIC NODULAR GOITERS

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In recent years the widespread publicity given to the subjects of cancer detection and prevention, the emphasis on periodic physical examinations and the development of cancer detection centers has resulted in an increased cancer consciousness in the population at large and in the medical profession. Therefore, physicians are being consulted oftener regarding the potential malignancy of benign lesions. Notable among these are nontoxic nodular goiters.

Few physicians would deny that firm discrete adenomas of the thyroid should be removed. The controversial question is whether to advise removal of soft nontoxic nodular enlargements of the thyroid. Many of these goiters are not enlarging or causing symptoms, and the patients often are unaware of their presence until they are found on a routine physical examination.

EXPLANATION OF THE HIGH REPORTED INCIDENCE OF CARCINOMA OF THE THYROID

There is a discrepancy between the high incidence of cancer of the thyroid [1] encountered by surgeons and the low incidence of fatal cancer of the thyroid reported in vital statistics.[2] Although surgeons often state that 5 to 10 per cent of nontoxic nodular goiters are malignant, this does not reflect the true incidence of cancer of the thyroid in this condition.[3] The incidence of malignancy, as observed by the surgeon, is high because he is dealing with the selected group of nontoxic nodular goiters that are subjected to thyroidectomy.

The patients who come to the surgeon have been carefully screened, first by the patient himself, who does not often consult a doctor unless the nodule is giving evidence of growth or functional activity; second by the family physicians or internist who detects the obvious benign quality of soft poorly defined involutionary nodules in the thyroid and hesitates to advise operation, and finally by the surgeon himself, who recognizes the innocuousness of small soft multinodular goiters, reassures the patient and discourages operation. Therefore, the fact that the surgical pathologist finds 8 per cent of nontoxic nodular goiters malignant merely means that this proportion of suspicious adenomas was proved to be cancerous. In the millions of nontoxic, symptomless and innocuous goiters which never are removed, the incidence of carcinoma is so low that vital statistics rate cancer of the thyroid sixteenth in the list of organs affected by malignant disease.[4]

Another cause for the discrepancy between the surgeons' and the internists' statistics is the confusion as to what constitutes a carcinoma of the thyroid. For example, some small carcinomas of the thyroid may exist for many years without enlarging or causing serious symptoms.[5] Such tumors may escape detection because the thyroid is not examined routinely in all autopsies. This may explain the difference between the incidence of carcinoma of the thyroid as reported by the surgical pathologist and that observed by the pathologist who confines his work to postmortem examinations and who does not examine the thyroid unless there are special indications.

A third cause of variation between the surgeon's statistics and those of the internist is the method of presentation of facts. An erroneous impression as to the frequency of carcinoma of the thyroid in solitary nodules may be conveyed by inclusion in the statistics of all frank carcinomas of the thyroid, even when the clinical diagnosis is clear and when widespread metastasis is present. This is as misleading as it would be to include all ulcerating carcinomas, regardless of size, infiltration or metastasis, in a survey of the malignant potentialities of benign gastric ulcer, and to exclude from this survey all gastric ulcers which healed under medical treatment and were not resected. The clinical carcinomas have been added to the total, and the obvious benign lesions that were not operated on have been subtracted from the total, with the result that the figures, although accurate, create a false impression.

PRESENTATION OF MATERIAL

As an indication of how the presentation of material may influence the statistical conclusion, we have analyzed our experience with carcinoma of the thyroid.

In a series of 768 thyroidectomies thirty malignant tumors were found, an incidence of 3.9 per cent. During this same period five inoperable malignant conditions of the thyroid were encountered, three of which have been excluded from this study because the clinical diagnosis was not confirmed by biopsy. The incidence of malignant tumors in all nodular goiters (with and without hyperthyroidism) was 5.6 per cent (table 1). Ten and nine-tenths per cent of nontoxic goiters were malignant, as well as 24.5 per cent of the solitary tumors.

A definite diagnosis of malignancy was made preoperatively in 27 of the 30 patients with confirmed

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malignancy of the thyroid. In 2 more cases the diagnosis of malignancy was suspected but not favored. In only 1 case was malignancy not diagnosed or suspected preoperatively (table 1). In this case a nodule was removed because of its hardness and proved to be a papillary carcinoma.

These data lend themselves to several forms of misleading deductions. It can be shown, for example, that carcinoma of the thyroid is commonly present in apparently innocent solitary adenomas. Three of 30 proved carcinomas occurring in 98 solitary nodules of the thyroid were not definitely diagnosed before operation. It would be correct to state that over 3 per cent of the solitary nodules that we have removed proved to be carcinomas undiagnosed before operation. On the basis

TABLE 1.—*Incidence of Malignancy in Nodular Goiter (1937-1946)*

	Incidence of Malignancy
I. In 537 nodular goiters (toxic, nontoxic, benign and malignant) 30 malignant tumors were present	5.6%
A. In 263 nodular goiters with hyperthyroidism no malignancy was present	0.0%
B. In 274 nodular goiters without hyperthyroidism 20 malignant growths were present	10.9%
1. Of 176 multinodular goiters, 6 were malignant	3.4%
2. Of 98 solitary tumors, 24 were malignant	24.5%

TABLE 2.—*Accuracy of Preoperative Diagnosis of Malignancy in 537 Nodular Goiters*

98 solitary tumors without hyperthyroidism	24 malignant growths	21 definitely diagnosed preoperatively
		2 suspected but not diagnosed preoperatively
		1 not suspected or diagnosed preoperatively
	74 benign tumors	61 diagnosed as benign
		13 suspected of being malignant but proved benign
		0 diagnosed as malignant but proved benign
176 multinodular goiters without hyperthyroidism	6 malignant growths	6 definitely diagnosed preoperatively
		0 suspected but not diagnosed preoperatively
		0 not suspected or diagnosed preoperatively
	170 benign tumors	164 diagnosed as benign
		6 suspected of being malignant but proved benign
		0 diagnosed as malignant
263 nodular goiters with hyperthyroidism	0 malignant growths	262 diagnosed as benign
		1 suspected of being malignant but proved benign
	263 benign tumors	0 diagnosed as malignant

of these statistics a patient with a solitary nodule in the thyroid could be informed that there was one chance in thirty that the tumor was malignant, even though there was no clinical evidence of cancer.

Approaching the subject from a different angle, it can be proved unlikely that a solitary nodule contains an unsuspected carcinoma. Although the diagnosis was not made before operation in 3 of the 98 cases, it was suspected in all but 1. Hence it would be correct to say that unsuspected carcinoma was found in only 1 per cent of the solitary nodules of the thyroid (table 2).

To estimate the true incidence of carcinoma of the thyroid it is necessary to know how many patients with solitary nodules were observed at the Cleveland Clinic during the same period. Analysis of the charts of 500 consecutive patients, excluding those who entered with the complaint of thyroid disease, or in whom operations on the thyroid were advised or performed, indicates that approximately 4 per cent had symptomless nodular goiters. These were incidental observations of the physical examination. Of those with nodular goiters about 25 per cent appeared to have solitary nodules. By projecting this experience over the period of observation, approximately 1,237 patients with solitary nodules of the thyroid probably have been examined and advised against having the goiter removed. It is impossible to state how many, if any, of these nodules subsequently proved to be malignant. However, we have not yet encountered a carcinoma of the thyroid in any of these patients. The claim might be made, therefore, that the incidence of unsuspected carcinoma of the thyroid in innocuous-appearing solitary adenomas is 1 in 1,335 (1,237 not operated on plus 98 operated on). This is a fallacious line of reasoning because there is no proof that ultimately some carcinomas will not appear.

Most of the carcinomas which are not suspected or diagnosed before operation are of the slowly growing, highly differentiated type. Since most of these are curable even after they have been present for years, and most of the undifferentiated carcinomas are incurable regardless of how early they are removed, it is not likely that earlier recognition and removal of carcinomas would alter the ultimate prognosis in more than 1 case in 5. Thus, if we were to institute a policy of removing all solitary adenomas of the thyroid regardless of history, size or consistency, we should have to remove 6,675 (5 times 1,335 total patients with solitary nodules) solitary adenomas to prevent 1 patient from dying of cancer. Regardless of the safety of thyroidectomy, it is doubtful whether 6,675 goiters could be removed without more than 1 postoperative death. This does not take into account the morbidity from technical accidents or the economic aspects of operation performed on such a scale.

Such deductions as these, which are based on statistical surveys of unfollowed cases, are clearly misleading. Conclusions regarding the innocuousness of nodular goiters based on reasoning such as this are as mistaken as would be the opposite if based only on selected surgical cases. Until we know more accurately how often benign adenomas become malignant it would seem wise to base indications for thyroidectomy on clinical judgment rather than on statistical surveys of selected or unfollowed cases.

COMMENT

Surgeons realize that conservative treatment of adenomatous goiters is frequently unwise. Often a patient with a hard enlarging tumor of the thyroid has been reassured by a physician, given a little iodine and advised to disregard the goiter. Such tumors are often malignant, and delay in treatment may prevent cure. These occasional errors have encouraged an overstatement of dangers of carcinoma of the thyroid in nodular goiter. Surgeons who suggest that all nodular enlargements of the thyroid should be removed regardless of history, physical observations or the apparent benign quality of the involutionary nodules are conscientiously attempting to give their patients maximum protection against carcinoma. However, indiscriminate thyroidectomy, performed on every one with nodular goiter, probably would entail a morbidity and mortality quite out of proportion to the number of cases of fatal cancer that it might prevent.

An enlarging adenoma of the thyroid, an adenoma which is firm and of different consistency from the rest

of the gland or one which is giving pressure sensations denoting growth should not be disregarded. Conspicuous adenomas should be removed for cosmetic reasons. All adenomas in children must be regarded with grave suspicion, as must discrete adenomas in adults, regardless of age. However, small soft nodular enlargements which have been examined and considered innocuous by a physician thoroughly familiar with diseases of the thyroid may be disregarded. Removal of such goiters is not justified and is comparable to indiscriminate removal of uteri and breasts for minimal benign lesions.

The physician who has not had considerable experience may have difficulty in recognizing the possible malignancy of a tumor of the thyroid. For this reason it is urged that the decision relative to removal of a tumor of the thyroid should be made by a physician or surgeon particularly qualified by experience and training.

Carcinoma of the thyroid is not necessarily a disease of old age. Since the tumors appear before the age of 20 in about one fourth of the patients with papillary carcinoma, and since the average age of patients with papillary carcinomas and lateral cervical metastasis is only 31.9 years, it is important to remember that a tumor of the thyroid in a child is more apt to be malignant than in a woman of 70. Carcinoma is almost as common in young adults as it is in older persons.

The presence of carcinoma cannot be excluded merely because the tumor has remained the same size. A tumor which has already metastasized to many cervical nodes may not enlarge for years and may never metastasize from the neck. For more than twenty years we have observed a patient with proved metastasis from a papillary carcinoma of the thyroid who has refused all treatment. The nodules in the thyroid and lateral cervical region are only a little larger than when they first appeared twenty-seven years ago.

Most malignant tumors of the thyroid are hard, or at least firm, and usually are of a different consistency than the nontumorous thyroid. The firmness and discreteness of the tumor is the most reliable indication in establishing suspicion of carcinoma of the thyroid.

Although the incidence of carcinoma is higher in nodular goiters, it is difficult to prove that carcinomas have their origin in benign adenomas. It is reasonable to suppose that many, if not most, carcinomas of the thyroid are carcinomas from the beginning and arise from the parenchyma of the thyroid as do benign adenomas. There is little proof that a benign tumor of the thyroid becomes malignant oftener than the goitrous thyroid parenchyma.

Since we cannot prove that carcinomas of the thyroid often arise within the substance of a benign adenoma, and since the incidence of carcinoma of the thyroid is so low, even in areas in which endemic goiter is prevalent, there is little possibility that a given adenoma of the thyroid will become malignant. The pertinent concern is whether or not the adenoma is cancerous at the time of examination. There is probably less chance that a benign adenoma will become malignant at some future date than that carcinoma will develop in the apparently normal uterus or breast.[6]

6. Fatal carcinoma of the breast is more than thirty times as common as fatal carcinoma of the thyroid (Incidence of Cancer, American Cancer Society, 1949). Carcinoma of the thyroid is only about seven times as common in areas of endemic goiters as it is in nongoitrous areas (Ward. R.: Malignant Goiter; Survey of Geographical Types, West. J. Surg. **43**: 494-504 [Sept.] 1935). In the goitrous thyroid, therefore, carcinoma does not develop as frequently as in the apparently normal breast.

The conventional subtotal thyroidectomy performed "prophylactically" for nontoxic nodular goiter does not give more than partial protection against the subsequent development of carcinoma in the remnants of the gland. A rapidly growing and fatal carcinoma of the thyroid has been observed to develop in a patient who had undergone "prophylactic" thyroidectomy thirty years before.

No surgeon would willingly subject a patient with a presumably benign goiter to the certainty of myxedema and the risk of tetany, which are involved in a total ablation of the thyroid. Remnants of the thyroid tissue remain after "prophylactic" subtotal thyroidectomy, and since these remnants have been subjected to the same pathologic stimulation that originally caused the development of the adenoma, a further development of adenomas or carcinomas is always possible. Moreover, a malignant tumor may be overlooked and left in the remnants of the thyroid. We have removed a papillary carcinoma of the thyroid less than a year after a "prophylactic" thyroidectomy had been performed for adenomatous goiter without hyperthyroidism. Neither surgeon nor pathologist discovered the carcinoma at the first operation, although we feel certain that it must have been there at that time.

Thyroidectomy for nodular goiter should be accomplished in such a way as to remove completely any carcinoma which may be present. Unfortunately, the same surgeon who advises the removal of an adenoma as a prophylaxis against the development of carcinoma frequently leaves carcinomatous tissue just as he would leave normal thyroid tissue in operations performed for benign lesions. Since the tumor had not been completely removed, the operation has failed in its purpose.

Surgeons should accustom themselves to thinking of discrete tumors of the thyroid not as benign adenomas which may become malignant at some remote time but rather as tumors which may be cancerous at the time of operation. If they did this they would remove the entire tumor, and should the tumor prove to be a carcinoma the chances of cure would be increased.

SUMMARY

Ten and nine-tenths per cent of surgically removed nontoxic nodular goiters and 24.5 per cent of surgically removed nontoxic solitary tumors of the thyroid proved to be malignant. The diagnosis of malignancy was made or suspected and so recorded before operation in over 90 per cent of the patients with malignancy of the thyroid.

These figures can be so presented as to indicate that (*a*) over 3 per cent of nontoxic solitary nodules of the thyroid are undiagnosed malignant tumors or (*b*) there is only 1 chance in 6,675 that removal of a nontoxic solitary nodule in the thyroid will give protection against death from carcinoma of the thyroid.

It is impossible, without better definition of histologic criteria of malignancy and without better autopsy and clinical statistics on the incidence of adenomas and carcinomas of the thyroid, to make an accurate statistical report of the true incidence of carcinoma of the thyroid in nodular goiters.

The high incidence of carcinoma of the thyroid reported by surgeons is to a large measure dependent on the fact that the obviously benign nodules in the thyroid are screened out by the patient or by the internist and are not seen by the surgeon.

Solitary adenomas of the thyroid in patients of any age should be viewed with suspicion especially (*a*) in

children, (*b*) when enlarging or giving symptoms of discomfort or pressure, (*c*) when firm or hard and (*d*) when discrete and of a different consistency from the remainder of the thyroid. Adenomas large enough to be of cosmetic importance should be removed. Soft involutionary nodules in the thyroid, especially when multiple and not large enough to be conspicuous, can be disregarded if they are not enlarging or causing symptoms.

The majority of malignant tumors of the thyroid can be recognized or at least suspected if a high index of suspicion is maintained regarding discrete adenomas. The danger is not that a discrete adenoma may become malignant, but rather that it is already malignant. If a discrete adenoma of the thyroid is to be removed, the operation should be so designed as to remove all of the tumor and cure the cancer if it is present.

Until better statistics on the true incidence of carcinoma in adenomas of the thyroid are available, it is suggested that indications for removal of nodular goiters be based on clinical judgment rather than on statistical surveys.

ABSTRACT OF DISCUSSION

DR. CHARLES W. MAYO, Rochester, Minn.: I have known for a long time and have admired Dr. Crile. I admire him because he has no fixed ideas and he is capable of changing. I bring that up because he was of that school that believed for a long time that the aberrant thyroid did not have its primary locus in the lobe itself. There are three types of adenocarcinomas of the thyroid. There is the papillary type, the so-called aberrant type of thyroid. There is the adenocarcinoma which is contained within the adenoma of the thyroid itself, or it is outside the adenoma. There is also the diffuse type of adenocarcinoma. The first, or papillary, is low grade, and the second, within or just without the adenoma, is of an intermediate grade. The diffuse type is usually a high grade type of adenocarcinoma. The papillary is considered more radiosensitive than the others. My co-workers and I have also an occasional case of sarcoma of the thyroid. Another unusual type is the squamous cell tumor of the thyroid, and we occasionally also see metastasis in the thyroid. I remember a case in which there was a carcinoma of the sigmoid metastasized to the thyroid. While statistics are not the aim alone, there is no study of any subject in medicine which does not entail the analysis of statistics. A review that Dr. Black made of cases between the years 1936 and 1945 showed that at the Mayo Clinic we see about 4.6 per cent carcinomas in the adenomatous type of gland. Dr. Kennedy made a study of children, and it was his observation that in patients under the age of 15 with single adenoma one third of the growths were malignant. I agree with Dr. Crile that the preoperative diagnosis has to be made on a clinical basis. I congratulate him on his figures, on the accuracy of the diagnosis preoperatively. Over 90 per cent is a very high rating on accuracy. I think that most of the histories, however, will show the suspicion rather than the accurate diagnosis preoperatively, which, after all, is approximately the same. But still we do see many as a pathologic surprise—a surgical surprise. I agree with Dr. Crile's philosophy as he expressed it in connection with dealing with these adenomas and the question of malignancy in thyroid disease.

DR. WARREN H. COLE, Chicago: At the Illinois Research Hospital our figures on the incidence of carcinoma of the thyroid are very similar to those reported by Dr. Crile and perhaps should be, since the patients in both series come from the Great Lakes goiter belt. Our incidence of carcinoma in solitary nontoxic nodular goiter over an eleven year period was 24.7 per cent compared with 24.5 per cent in his series. However, our incidence of carcinoma in our entire series of 274 solitary and multinodular nontoxic nodular goiter was 17.15 per cent as compared with 10.9 per cent in his series. The difference lay in a greater incidence of carcinoma in multinodular goiter in our series, namely, 9.0 per cent compared with 3.4 per cent in his series. The incidence of carcinoma in toxic diffuse and toxic nodular goiter is so low (only a fraction of 1 per cent in the former and only slightly greater in the latter) that we should not include these types in our figures.

The incidence of carcinoma in our series should no doubt be larger than Dr. Crile's because all of our patients are charity patients, whereas most of his are private patients. Charity patients do not come to the physician as soon as do private patients. Our series show that the danger of carcinoma is much greater in nontoxic nodular goiter in male than in female subjects and slightly greater in white than in Negro subjects. I agree with Dr. Crile that the percentage of carcinoma in thyroidectomy specimens is not a true index of incidence. However, the screening in our series must be attributed only to the patients, and not to the doctors, because my co-workers and I have advised operation for all solitary nontoxic nodular goiters since our first report dealing with data up to January 1944. With few exceptions, all our patients have consented to operation. Nevertheless, this policy has not decreased the incidence of carcinoma in this group. The slight change noted was actually an increase, namely, from 24.0 per cent (1936 to 1943) to 25.5 per cent (1944 to 1947) carcinoma in cases of solitary nontoxic nodular goiter. The criticism has often been made of reports on incidence of carcinoma of the thyroid that the criteria of diagnosis have not been sufficiently strict. From the data obtained in our series at Illinois Research Hospital it appears that we have a very good answer to this criticism. Of the 16 cases of carcinoma of the thyroid treated here during the past four years, we have been able to follow 14. Of these 14 patients, 10 are already dead, presumably of metastases. An additional patient has metastases, but is still alive. We know that most of these deaths were of carcinoma, but cannot prove that all were, although, since patients with carcinoma of the thyroid are relatively young, it is not likely that many of them died of natural causes.

DR. GEORGE CRILE JR.: Dr. Mayo mentioned the subject of fixed ideas. I think that thyroid is a subject on which it is very difficult to have any fixed ideas today, and I think that anyone who does have them will be in trouble because of the changes due to new methods of treatment. Dr. Mayo made one statement which I do not question because I am not in a position to do so, but I believe that it requires some proof; that is, the sensitivity of the papillary type of carcinoma to irradiation. Our experience has been that these tumors are not uniformly sensitive to irradiation. A misleading impression may be obtained because these tumors are of such low malignancy that they may be present for many years without enlarging at all, with no treatment. I emphasize this because I think that surgeons should not rely on roentgen rays in these cases. These are the most favorable cases from the surgical point of view, and one should attempt to eradicate these papillary tumors by surgical removal. With respect to the carcinomas that are not recognized before operation, I should like to point out also that there is a type of tumor in the thyroid which has been designated as an adenocarcinoma and which histologically is typical of that. These are the tumors which have been reported by Graham, Goetsch and recently by Black and others, which are only 1 or 2 cm. in diameter and are often found in diffuse hyperplastic glands. These are also found at autopsy, and their presence is rarely noticed prior to operation. They rarely, if ever, recur or metastasize and are of questionable malignancy. It has been our experience that the majority of undifferentiated rapidly fatal carcinomas of the thyroid, such as Dr. Cole must have been dealing with in this group of cases, arise without warning in thyroids that were previously considered normal. The patient may not have even been aware that there was any tumor in the thyroid, and by the time the doctor sees them they are usually incurable. I do not mean to be pessimistic about prophylactic operations. I emphasize again that nodules of the thyroid and tumors of the thyroid have malignant

potentialities. I do not believe that a 90 per cent accuracy of preoperative diagnosis can be maintained. Since these figures have been prepared I have missed 1 or 2 cases, and I am sure that I and everybody else will miss others. But I think if one carries a high index of suspicion of a solitary nodule one will have the correct attitude at the time of operation to eradicate the tumor if it turns out to be malignant.

ABNORMAL BLEEDING

Response to Treatment with Toluidine Blue and Protamine Sulfate

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Hemorrhage arising from abnormal hemostasis is often complicated in origin and troublesome to treat. Bleeding may occur from a single disturbance in the plasma clotting mechanism, in the platelet quantity or in the integrity of the vascular wall. More frequently, spontaneous bleeding is associated with several disorders in one or more of these systems.

Reported herein are summarized data on a series of patients with spontaneous bleeding who had a similar clotting abnormality. This clotting defect was characterized by an increase in the protamine titration [1] and was frequently associated with a prolongation in the whole blood clotting time.[2] Many of these patients also had thrombopenia of moderate or severe degree.

The nature of the defect revealed by the protamine titration resembles, but is not identical with, that produced by the intravenous injection of commercial beef heparin.[2] Moreover, the protamine titration may be influenced by factors other than heparin; in fact, it is probably increased by any disturbance which interferes with fibrin formation; i. e., hemophilia and reduced prothrombin.

The blood of the patients comprising this study showed an increased protamine titration when the prothrombin level was normal or near normal, when fibrinogen levels were not abnormal and when fibrinolysin was not grossly disturbed. Although many of these patients had thrombopenia, this was an associated disturbance and was independent of the protamine titration.[3] Only rarely was the clotting time of whole blood of these patients sufficiently prolonged to delay appreciably the clotting of normal blood.

As will be shown in the data to follow, the bleeding of many of these patients appeared to respond to the administration of toluidine blue and/or protamine sulfate. These substances are antiheparins but are capable of reacting with other biologic compounds. A detailed report of this material is presented elsewhere.[4]

Methods of study in these patients included determination of the whole blood clotting time,[2] the protamine titration,[1] erythrocyte, leukocyte and thrombocyte counts, measurement of prothrombin activity,[5] and gross observation for clot retraction and fibrinolysin.

CLINICAL OBSERVATIONS

In the table are listed a number of patients with a variety of hemorrhagic disorders. As will be noted, the protamine titration was increased in all these patients, although not all responded to toluidine blue or protamine sulfate. In some, the increased protamine titration was due to hemophilia; in others, it was due to pronounced prothrombin deficiency. Neither of these groups responded to toluidine blue or protamine sulfate. The patients who did respond had neither an extreme prothrombin deficiency nor hemophilia, but they did have an increased protamine titration. It is obvious that the random use of toluidine blue and/or protamine sulfate in the treatment of hemorrhage will lead to random results. It is necessary that each patient with a bleeding tendency be studied as completely as possible with reference to the status of the hemostatic mechanism if therapy is to be correctly applied.

Abstracts of the histories of 6 patients, representative of some of the group with hemorrhagic disorders in whom this heparinoid defect in the clotting mechanism appeared to contribute to bleeding, are presented.

REPORTS OF CASES

CASE 1.—*Postpartum Bleeding.*—A 25 year old woman was admitted to the Chicago Lying-In Hospital and delivered spontaneously sustaining a second degree laceration of the perineum which was repaired with chromic surgical gut. The course of her illness was uneventful until the fourth postpartum day, when bleeding occurred from the perineal laceration. This area was resutured, but bleeding occurred at the site of each new suture. In addition, and probably accounting for most of the loss of blood, two large bleeding vessels were found in the old repair site. These were clamped; the mucous membrane was approximated with a continuous no. 0 chromic surgical gut suture, and a pack was applied. Some oozing continued.

The patient, whose blood was Rh negative AB, received 600 cc. of Rh-negative type O blood at the end of the operative procedure. Fifteen minutes after the transfusion she had a mild chill and voided urine containing hemoglobin. Although the volume of urine was reduced and the blood nonprotein nitrogen rose to 100 mg. per hundred cubic centimeters by the ninth postpartum day, complete recovery occurred.

Twelve hours after the hemorrhagic episode and ten hours after the transfusion, coagulation studies were made (fifth postpartum day) which showed the protamine titration increased to 0.400 mg. (normal value, 0.140 mg.), the whole blood clotting time in excess of three hours, the platelet count at 260,000 per cubic millimeter, and prothrombin activity at 54 per cent of normal. In addition, fibrinolysin was prominent. All clots completely lysed in less than 30 minutes once they formed. There was no evidence of fibrinogenolysin. Because of the severely prolonged whole blood clotting time, the greatly increased protamine requirement in the protamine titration and the presence of fibrinolysin, 6 mg. per kilogram of body weight of toluidine blue and 3 mg. per kilogram of protamine sulfate were given separately intravenously over a two and one-half hour period. Two hours after the toluidine blue and protamine sulfate were given, the whole blood clotting time was thirty

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