obstruction which so often occurs, and the post-operative mortality is increased 50 per cent by this complication. Reduction of the hernia and repair of the diaphragm are accomplished either through laparotomy or thoracotomy, and sometimes a combination of both incisions is necessary. Abdominal approach is very much to be preferred, so as to enable one to explore the abdomen for other pathological conditions, and to deal with any complication of the herniated viscera, if present, such as an ulcer of the stomach, as in the case where Harrington[9] had to do a partial gastrectomy. In recent traumatic cases the thoracic approach is more suitable. In large hernias where there has been avulsion of part of the diaphragm from the chest wall, or where destruction of diaphragmatic substance has occurred, Harrington paralyzes that half of the diaphragm either temporarily or permanently by doing a phrenicotomy, and reports excellent results in suitably chosen cases.

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AN APPARENT INSTANCE OF PARATHORMONE INACTIVITY*

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IN May last Lowenburg and Ginsburg[1] published an account of the apparently successful treatment of two cases of primary purpura (thrombocytopenic purpura) by prolonged hypercalcæmia induced by repeated injections of parathormone. Their results led to the use of parathormone in the case we now review. We wish to stress at the outset the fact that the non-success here recorded must in no way be regarded as adverse to their findings. The purpura in the case presented here was secondary and of undetermined origin, while hypercalcæmia was not induced by the parathormone therapy.

We give first the essential features of the case report, and then discuss its implications.

CASE REPORT

A graduate nurse, aged 26, employed on floor duty at the time of her illness, was first seen on June 15, 1936, complaining of small hæmorrhages under the skin. She was then, apparently, in fair health; she had, for example, played tennis the previous day.

History of illness.—On June 10th she had observed pin-point hæmorrhagic spots in the left side of her neck, the volar aspects of her forearms, and the anterior tibial region of her left leg. She had noticed that she bruised more easily than usual; such slight causes as placing her elbow on a table produced a black and blue area the size of a fifty-cent piece. Enquiry elicited that she had had epistaxis intermittently since the early part of May. She had consulted a dentist for bleeding gums on May 28th and on June 6th. Her last menstrual period on May 25th was unusual in that she had a very profuse flow, passing many clots. Up to this time her menstrual periods had invariably been regular, with moderate flow. For the past year she had tired easily, and had found it difficult to keep up with her work. She was aware that her pulse rate had increased to 100, seldom dropping as low as 80.

While she had been in training routine chest plates had shown areas of calcification in both hila and also to a certain extent in the lung fields. She had therefore been kept under observation, and x-ray plates were repeatedly made, but at no time was there any evidence of tuberculous activity.

Physical examination.—A thorough physical examination (June 16th) gave the following positive findings. There were areas of petechial hæmorrhage on the neck, the volar surface of both forearms, the dorsal surfaces of both hands, the inner aspects of both thighs, and the anterior tibial region of the left leg, with scattered spots on the chest and abdomen. Most of these hæmorrhages were situated in hair follicles, but the remainder seemed to have no definite relationship to the skin structure. In addition there were larger areas of subcutaneous bleeding up to the size of a silver dollar; these all had a traumatic basis. The teeth and tongue were healthy, and the mucous membrane of the mouth was healthy except for some oozing of blood from the gingival margin. There were a few scattered petecheal spots on the inner aspect of the cheeks and on the roof of the mouth. A few crusts of dried blood were present in the left nostril (due to a nose-bleed on the previous day).

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The thyroid showed a slight, diffuse enlargement. The spleen and liver were not palpable. Blood pressure, 118/76. There were no other significant findings.

The laboratory findings at this time were: Urine: specific gravity, 1.022; sugar and albumin absent; blood and bile absent; an occasional pus cell present. Blood: 3.56 million red cells, slight anisocytosis, otherwise normal; 65 per cent hæmoglobin; colour-index 0.92; 6,000 white cells; polymorphonuclears 75, small lymphocytes 24, and monocytes 1 per cent; reticulocytes 0.65 per cent; platelets 100,000; icterus-index 5; clotting time 7 minutes; bleeding time 35 minutes, followed by intermittent bleeding for 6 hours. Stool: negative for blood.

The patient's condition caused no immediate alarm. It was thought that she had a secondary purpura, possibly anaphylactoid, though the skin lesions did not suggest this. She was kept in bed on normal diet, and calcium gluconate was given, 10 grains thrice daily.

Clinical history June 17th to 19th inclusive.—There was intermittent oozing from nose and gums throughout this period; on the 17th a hæmatoma developed in the left cheek, gradually increasing in size, and ulcerating on the 19th. The tourniquet test was positive, 3 minutes on the 17th, and 4 minutes on the 19th. Stools were positive for occult blood on the 18th and 19th. On these dates the (soft) clot showed no retraction in 20 and 23 hours respectively. The platelet count was 150,000 on the 18th (and again on the 20th). There was some diarrhœa on the 18th and 19th.

On the 18th 35 c.c., and on the 19th 40 c.c. of unmatched blood were injected intramuscularly. This treatment produced transient cessation of hæmorrhage.

June 20th to 23rd inclusive (parathormone period).—Though it was realized that the case was not one of thrombocytopenic purpura it was decided to try parathormone therapy. Prior to injection serum calcium was 10.2 and inorganic phosphorus 2.7 mg. per 100 c.c. (10.45 a.m. on the 20th).

Intramuscular injections of parathormone (Lilly) were given at 12.25 p.m. on June 20th (60 units); at 1.50 p.m. on June 21st (60 units); at 4.30 p.m. on June 22nd (80 units); and at 3.45 p.m. on June 23rd (100 units). With the first injection 10 c.c. of 10 per cent calcium gluconate were also injected, while calcium gluconate was also given orally in small dosage throughout the whole period of treatment.

The morning figures for serum calcium were 10.2 (June 22nd) and 9.3 (June 23rd); that for inorganic phosphorus on the 22nd was 2.4 mg. per 100 c.c. The corresponding figures on the morning of the 24th were 8.8 and 2.9 mg.

Nausea and vomiting occurred at 4 p.m. on the 20th, three and one-half hours after the first injection of parathormone. Nausea was complained of two or three hours or even earlier after each injection; it persisted for many hours. Abdominal cramps were frequently complained of. During such an attack at 10.30 p.m. on the 20th the patient vomited 4 oz. of old blood. There was subsequently no vomiting until 6.15 p.m. and again at 8 p.m. on the 23rd. There was no diarrhœa during these four days.

On the 21st bleeding from the gums had lessened. At 8 p.m. menstruation commenced, at approximately the expected period. Nausea (with headache) persisted. The menstrual flow was very profuse throughout the night of the 22nd, requiring two to four pads an hour. (Headache and nausea were features during this period.) On the 23rd one or two pads were needed throughout the day, but at 8 p.m. menstruation had practically ceased. At this time there was severe headache, and a difficulty with speech had been noticed (though speech was normal on the following day). During the menstrual period bleeding from the gums and nose ceased, but it recommenced on the night of the 23rd. The stool was positive for blood on the 22nd.

The anæmia increased steadily. On the 22nd blood examination showed 2.42 million red cells, with 40 per cent hæmoglobin; 7,700 white cells, and 290,000 platelets, with a bleeding time of 24+ hours, and no clot retraction in 23 hours, though the clot was firmer. On the 23rd there were 2.13 million red cells, with 35 per cent hæmoglobin.

June 24th to 26th inclusive.—At 8.45 a.m. on the 24th, blood examination showed 1.63 million red cells and 25 per cent hæmoglobin, with 210,000 platelets. A transfusion of 550 c.c. whole blood was given one and one-half hours later. The patient had a fairly good day, though weak and tired. At 11 p.m. speech was incoherent. All hæmorrhages had stopped except for slight oozing from the gums. During the night bleeding recommenced (from gums, nose, and vagina).

At 5 a.m. on the 25th the patient was irrational and listless; at 8 a.m. she had severe headache and was very depressed. Perspiration was profuse during this period. At 10 a.m. blood examination showed 2.15 million red cells and 42 per cent hæmoglobin. Serum calcium was 9.2; inorganic phosphorus 2.5 mg. per 100 c.c. She had difficulty with her speech but was rational. A right-sided hemiplegia had developed. Vomiting was continuous. At 3 p.m. she was unable to articulate and was irrational. There was bleeding from gums and vagina. Blood pressure at 6 p.m. 110/68, at 11 p.m. 106/60, and at 4 a.m. on the 26th 135/65. The patient died three hours later.

Temperature, pulse and respiration.—No definite relationship could be established between these and the condition of the patient. On admission her temperature was 99° F., and a low-grade temperature persisted throughout the illness, with maxima slowly rising to 102.2° F. at 8 p.m. on the 23rd. The pulse varied from 75 to 95 at first, rose to 105 on the morning of the 20th, and subsequently varied between 95 and 130. There was no change in the respiratory rate until just before death.

Summary of autopsy findings (Professor Wm. Boyd).—Numerous small hæmorrhages were scattered over the pericardium and pleura. The ovaries and the endometrium were sites of hæmorrhages. There was no corpus luteum in either ovary. The most striking hæmorrhages were in the brain. Microscopically, these were found to be in the nature of a transudation through capillaries, the endothelium of which was greatly degenerated. The cervical and mesenteric lymph nodes were slightly enlarged and greatly congested. They showed the swelling and degeneration of germinal centres commonly associated with status lymphaticus. No changes could be detected in the parathyroids and the pituitary.

DISCUSSION

The cause of the purpura was not ascertained. The continuous low-grade temperature suggests that some undetermined bacterial infection may have been an associated factor. The profuse menstruation, first experienced a month earlier, suggests the possibility of an endocrine factor, but such profuse menstruation has been frequently reported in cases of purpura, and is probably due to the condition itself. The absence of corpora lutea suggests that the menstruation may have been of the anovulation type.

It would serve no useful purpose to discuss further the many theoretical possibilities as to

the etiology of the purpura. The salient findings, as far as the present enquiry is concerned, are shown in Chart 1.

The bearing of this case upon parathormone therapy can perhaps be most simply discussed under the following heads: (1) the effects of parathormone administration as recorded in the literature; (2) the toxic effects of parathormone overdosage; (3) the effects of profuse hæmorrhage and of menstruation upon the

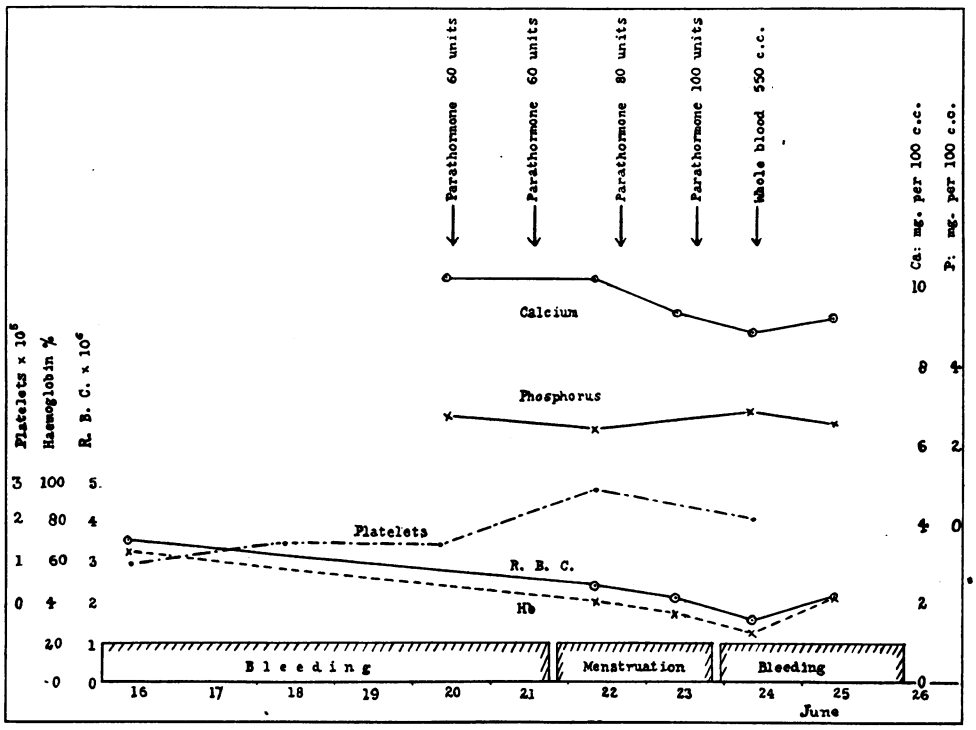

Chart 1

serum calcium of the blood; and (4) possible causes of the apparent ineffectiveness of parathormone in this case.

The effects of parathormone administration.— A comprehensive, although certainly incomplete, search of the literature recording the effects following injections of parathyroid extracts (usually that preparation known as parathormone) into animals and man, since Collip first obtained a concentrate of the parathyroid principle sufficiently potent to be of clinical value, permits the following statements.

In the dog a rise of blood (serum) calcium is produced rapidly, following the injection of parathormone intravenously, and less rapidly, but to a higher level, following subcutaneous or intramuscular injection. The inorganic phosphorus of the plasma is usually but little affected with small dosage. Similar results are obtained with man.[2]

With both man and the dog marked quantitative differences of effect on blood calcium are obtained, both in different individuals of the same species, and in the same individual at different times.[2, 3] Other species, such as the cat, rabbit, guinea-pig, and rat, and various species of birds are less affected,[4, 5] although in all of these species increases of blood calcium can be induced by parathormone under appropriate conditions.

In the dog, the rat, and man, refractoriness may develop to prolonged injections of the extract.[2, 6] The cause of this has not yet been determined, but no "anti-hormone" has been demonstrated for the parathyroid principle, and the development of tolerance to the principle is probably associated inherently with the mechanism of its action.[2, 7]

In the dog a single large dose, given subcutaneously or intramuscularly, is followed by a steady rise of serum calcium over many hours, the peak-time varying with the dosage; there is a fall at approximately the same rate; after 18 to 24 hours there is still, usually, a definite increase above the initial value. This also holds true for man. Repeated dosage

intensifies the effects. There is increased excretion of calcium and phosphorus. The chemical changes are due, chiefly, to mobilization of the solid material from bone by the direct action of the parathyroid principle.[2, 8]

If these, the usual results, are to be regarded as the normal effect of parathormone on man and the dog, then the following results reported in the literature are at least unusual, if not abnormal. The initial blood calcium was approximately normal in almost all of these cases.

Gordon, Roark and Lewis[9] noted that while in most patients they could maintain a serum calcium of between 12 and 14 mg. per 100 c.c. by daily injection of 10 to 20 units of parathormone, yet in two patients a lowered calcium level persisted for several days before the usual elevation commenced. Ellsworth and Howard[10] noted that in a proportion of their cases, following the intravenous injection of 40 units of parathormone, the serum calcium tended to fall rather than to rise. Merritt and Bauer[11] injected several hundred units of parathormone (two injections daily, with increasing dosage) into seven patients, during a four-day period. The usual rise in serum calcium was produced in five, but in the other two "no significant elevation in the serum calcium was observed, although larger doses of the same parathyroid extract which had been effective in the other five cases were used". These two received 485 and 550 units of parathormone respectively. No untoward effects are recorded for any of their cases.

Hunter and Aub[12] treated six patients for lead poisoning with steadily increasing doses of parathormone (injected two or three times a day) for periods of two weeks or more. Five of the six responded with the usual hypercalcæmia, although some showed greater effect than others. Thus one patient, on an average daily dose of only 45 units, was found after seven days to have a serum calcium of 19.8 mg. per 100 c.c., which was maintained (without further parathormone) for three days. It is noteworthy that during this period the patient was up and about, and complained only of slight nausea and loss of appetite; he showed no evidence of increased viscosity of the blood. None of their patients showed any ill-effects from the treatment. Their sixth patient showed practically no response to parathormone, so far as blood calcium was concerned. "No rise in blood calcium occurred after treatment for 15 days, on an average daily dose of 65 units. Later, on the same average dose, the blood calcium rose only to 10.8 after a period of 9 days . . . . This phenomenon by no means indicates an unsusceptibility to the effects of parathyroid, for the total calcium output in this man at this time distinctly increased. This . . . . indicates that the increased calcium excretion is not dependent upon a raised calcium level of the blood."

In the case we are reporting it will have been seen that the administration of 300 units of parathormone over a period of four days caused a steady fall of serum calcium from 10.2 to 8.8 mg. per 100 c.c. (Hunter and Aub's case actually showed a drop from 9.2 to 8.0 mg. in the first five days.)

The toxic effects of parathormone overdosage.—These have been most carefully studied in the dog. Collip found them to be, in order of development, vomiting and diarrhœa, some uneasiness, depression, respiratory distress, passage of blood by the bowel, thickening of the blood, cessation of kidney function, and finally death. Post-mortem examination shows marked congestion of the alimentary canal and presence of blood in the stomach and intestine, with petechial hæmorrhages in the gastrointestinal mucosa.[13, 14] Calcification has been observed, especially in the spaces of Bowman's capsules and the lumina of the tubules of the kidneys, and in the walls of the lesser arteries and the Küppfer cells of the liver.[2] Macleod and Taylor[15] considered that the earliest symptoms were lassitude, muscular relaxation, depression and weakness, and that these could appear with a serum calcium level of 15 mg. Collip[13] states that vomiting may occur when the serum calcium surpasses this level. Other manifestations, apparently associated specifically with the hypercalcæmia, are irregularities of the heart beat, and sometimes actual slowing of the heart with a fall in blood pressure,[16, 17] and a functional disturbance of the higher nerve centres, shown for example by an exaggeration of the inhibitory process and a varying degree of lethargy.[18]

The experimental results on the dog indicate that the more serious manifestations of parathyroid overdosage occur when the hypercalc-

æmia commences to decline from a peak value of the order of 20 mg. per 100 c.c., and a marked hyperphosphatæmia is developing. Bodansky and Jaffe[19] believe that in young pups anorexia, even in the absence of hypercalcæmia, can be considered as a reliable indication of overdosage and of the imminence of more urgent symptoms.

Man seems to be somewhat less susceptible to overdosage than the dog, though naturally fewer exact observations are available. Children seem more susceptible than adults. Brehme and Gyorgy[20] speak of pallor, vomiting, abnormal stools, apathy, drowsiness, disturbed circulation, nephritic disturbances, and sometimes death, following overdosage in children. Lowenburg and Ginsburg's[1] first patient, a boy of five years, accidentally received 100 units a day for six days, and developed extreme hypercalcæmia (19.6 mg. per 100 c.c. serum) without definite rise in plasma phosphates, but with alarming symptoms including vomiting, stupor, and high temperature.[21]

Bowman[22] stresses vomiting (in adults) as a danger signal of overdosage, even in absence of a hypercalcæmia definitely above normal. Johnson and Wilder,[23] after injecting 50 units daily for 12 days into a normal adult, noted the production of muscular weakness, pains in the bones and muscles, and dull headache. Lowenburg and Ginsburg[1] claim that the earliest toxic symptom is vomiting, which is shortly afterwards followed by weakness, apathy, and lethargy, even of speech. In the second of their cases, a boy aged 7, nausea and vomiting apparently developed with a serum calcium of 12.3 mg. and a blood inorganic phosphate of 5.4 mg. per 100 c.c. plasma.

With such results may be contrasted the complete absence of symptoms in the majority of treated cases, in which a serum calcium figure of 12 to 14 mg. or more has not infrequently been reached, and the almost complete lack of symptoms even in such a case as that of Hunter and Aub already cited, in which the figure 19.8 mg. was maintained for three days. In such cases hyperphosphatæmia is absent, and it is also not without significance that in the chronic hyperparathyroidism of osteitis cystica and related conditions, while marked hypercalcæmia is not uncommon a marked hyperphosphatæmia does not occur, and the symptoms of acute parathyroid poisoning are absent.

The variations in susceptibility to parathyroid poisoning seem as great as the quantitative variations in the chemical changes; the parallelism is suggestive, nor is there any good evidence that the former can occur in absence of the latter—that even vomiting, which certainly appears to be the earliest definite symptom, can be attributed to parathyroid poisoning unless it is accompanied by some definite degree of hypercalcæmia.

It is usually considered that the risk of parathyroid overdosage is adequately guarded against by determination of serum calcium at frequent intervals[2] and such a supposition seems justified by the very few records of toxic effects to be found in the literature. The incomplete agreement of these, however, suggests that there is need for further accurate record of all such cases, so that knowledge of the earliest symptomatology can be rendered more precise.

Careful analysis of the case under review permits the conclusion that it is very unlikely that the untoward events during the period of parathormone treatment and subsequently were in any way affected by that treatment. There was no hypercalcæmia, no hyperphosphatæmia, no thickening of the blood, no definite lessening of clotting time, no change in kidney function. The trend to higher temperature was antecedent to the treatment, the pulse was but doubtfully affected, and the respiration not at all.

The nausea which followed injection seemed to appear too soon to be definitely associable with parathyroid action. Vomiting was infrequent during the treatment, diarrhœa was absent, and the short period of incoherence of speech cannot be stressed. Such symptoms as vomiting, headache, increased temperature of the order recorded in this case, profuse menstruation, and cerebral hæmorrhage are not uncommonly recorded in the case reports concerned with purpura. The absence of improvement in any of the manifestations of the purpura is at once explicable by the absence of an induced hypercalcæmia.

The effects of profuse hæmorrhage and of menstruation upon the serum calcium.—Numer-

ous investigators have attempted to determine these effects. The pertinency of their findings to the present enquiry is obvious.

Severe experimental bleeding in animals raises the serum calcium.[24, 25, 26] Statements concerning the many cases of presumably normal menstruation that have been studied are somewhat contradictory, but the careful recent studies of Okey, Stewart and Greenwood[27] show that there is either no effect or that it is negligibly small. We have found no indication in the case reports that we have perused that parathormone administered during the menstrual period does not produce its usual effect. The careful prolonged study of Lisser and Shepardson[6] would surely have revealed any abnormal effect if it had occurred.

Profuse menstruation suggests a possible abnormal ovarian factor, but in our case it is much more likely to have been due to the purpuric condition itself (the first bleeding from nose and gums, and the first profuse menstruation all occurred in May). This renders of little interest to this discussion the somewhat inconclusive evidence that has been summarized by Zwarenstein,[28] that injection of potent ovarian extracts depresses the blood calcium.

Possible causes of the apparent ineffectiveness of parathormone in this case.—The chemical analyses were performed in duplicate and the duplicates showed good agreement. Clark and Collip's procedure was employed for calcium, and subsequent analyses of solutions of known calcium content confirmed the complete accuracy of the findings.

It was naturally desirable to exclude the possibility of inactivity of the actual preparation of parathormone used. Fortunately one vial (5 c.c.; 100 units) with the same serial number was available, and had been kept in an ice-box under like conditions as for the vials used for the patient. With the kind assistance of Prof. V. H. K. Moorhouse, of the Department of Physiology and Pharmacology, we were able to test this. Parathormone is standardized on dogs of about 20 kg. weight; the average effect on several dogs is such that 100 units produce a 5 mg. rise in serum calcium in 15 hours. We found that the vial reputedly containing 100 units raised the serum calcium of a 12.6 kg. dog 2.9 mg. in 16 hours. Hence the potency of the preparation was definite, and (remembering the great variability with different dogs) it was probably of the order stated.

The chief criterion suggesting ineffectiveness in this case was the lack of increase of serum calcium. It is indeed true that had blood been analyzed at more frequent intervals fluctuations during each day indicating transient increases might have been revealed; such increases would have been negligible compared with the usual effects of parathormone therapy; the slightly-falling curve in Chart 1 is completely different from that usually recorded. The non-production of a hypercalcæmia may have been due to a factor which counteracted the effect of parathormone on the blood calcium only, or which neutralized its whole action.

It is well recognized that infections lessen the effect of endocrine therapy, necessitating increased dosage; this has been well exemplified in the control of diabetics by insulin. In Lisser and Shepardson's case of tetania parathyreopriva[6] it was found that intercurrent infection raised the dosage needed to control tetany. Linder[29] has recently shown that the response to parathormone is lessened during typhoid fever. One of his patients showed practically no response, but the dosage was small. In the present case the low-grade temperature present throughout the illness indicated presence of an infection, but is seems unlikely that this would have completely nullified the action of parathormone. In most of the other cases cited an increased temperature does not appear to have been present. In most of Gordon, Roark and Lewis's tuberculous cases, with temperature, normal parathormone effects were produced.[9]

The hæmorrhage of menstruation has been considered as a factor and must be ruled out. An effect from ovarian hyperfunction is theoretically possible, but seems improbable in this case.

Hunter and Aub's case demonstrated that parathormone can cause increased excretion of calcium without a concomitant rise in blood calcium. In none of the other unusual cases that we have quoted was the calcium balance determined.

It has been suggested that the rate of excretion determines the degree of change in blood calcium,[5] and this may well account for

the differences observed in different species. Thus, while the rat is regarded as a resistant species, yet the increased urinary excretion of calcium in that animal is so definite that it has been suggested as a means of standardizing parathormone.[30] Bearing upon this point is the comment of Thomson and Collip:[31] "We consider that the combination of hypercalcæmia and hyperphosphatæmia is responsible for the more striking manifestations (of overdosage in the dog). Other species contrive to deal more successfully with the overflow of calcium, so that marked hyperphosphatæmia is not observed and congestion of the alimentary tract in not seen." The variation in the calcium excretion in man is also exemplified by the fact that less than half of the cases of chronic hyperparathyroidism develop kidney involvement, with resulting kidney stones or parenchymatous deposits of calcium phosphate.

We have, however, no clue to the factor or factors, physiological or pathological, which determine this variability of excretory function in individuals and in species. Certain investigators insist that administration of parathormone can produce a phosphate diuresis through direct action on kidney tissue.[32, 33] If this is true it may have some relation to the problem.

That other apparently unrelated agencies may be of significance is suggested by such incidental observations as the following. Hjort and Eder[34] reported that in a case of tetany following thyroidectomy even 130 units of parathormone a day had but little effect on the serum calcium until this treatment was supplemented by oral thyroid therapy (*cf.* also[6]). On the other hand, it is recognized that hyperthyroidism tends to increase calcium excretion and depress blood calcium. Also somewhat contradictory seem reports that parathormone produces a fall in the serum calcium of dogs rendered hypercalcæmic by excess of vitamin D,[35] and that it produces but little effect in pups on a diet deficient in this vitamin.[36]

It is to be hoped that further experimental work will throw some light upon the causes of the quantitative variations in responses to parathormone, and will thus permit a greater measure of control of parathormone therapy. In the meantime it seems to be a legitimate conclusion from this case that where parathormone is used to induce hypercalcæmia if there is no definite hypercalcæmic response within one or two days other therapy should be considered.

SUMMARY

In a case of purpura of undetermined origin the administration of parathormone produced practically no effect on blood serum calcium or inorganic phosphorus.

Cases in the literature which appeared to show similar lack of action are reviewed.

Possible causes of this apparent ineffectiveness are discussed.

In the control of parathormone administration by blood calcium determinations lack of production of some degree of hypercalcæmia within one or two days should be regarded as indication for consideration of an alternative therapy.

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THE SURGICAL ASPECTS OF ORAL CANCER

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WITH the introduction of radium in the treatment of oral cancer it was felt that a combined study of a group of cases would determine the exact rôle which radium and surgery might each play in the management of the disease. It was well known that surgical measures alone had proved disappointing, particularly in the intra-oral group of cases, and it was hoped a great improvement would follow the employment of radium. Accordingly, representatives of the surgical staff of the Toronto General Hospital have cooperated with the staff of the Radiological Department in the examination, treatment, and subsequent progress of all cases of lip and intra-oral cancers. A series of papers by Dr. Richards has recently appeared in this *Journal*. These have been based on a study of cases of oral cancer treated in the Institute of Radiotherapy, Toronto, in the years 1929 to 1935 inclusive. The primary lesions have all been treated radiologically, whereas both surgery and radiation have been employed in dealing with glandular and bone complications.

This paper is intended to be a critical review of the results of treatment not only of the primary lesions but more particularly of the disease as it affected the regional lymph glands and the neighbouring bones. The cases under review correspond almost exactly with those already presented by Dr. Richards, and consist of a series of 609 cases of oral cancer, of which 338 were cancers of the lip, 101 cancers of the tongue, and 170 cancers originating in the mouth elsewhere.

A few rather striking generalizations may be made. In the first place, oral cancer is very largely a disease of males. This is particularly true of cancer of the lip. In the second place, oral cancer tends to be a local problem, that is to say, the spread of the disease is to the lymph glands of the neck or neighbouring jaw, remote metastases being rare. The average age is over 60 years; in lip cancers 63, in cancers of the tongue 60.7, and in the buccal mucosa, 62.5. As in cancer elsewhere, the younger the subject, the more serious the outlook, the more rapid the growth, and the earlier the involvement of the lymph nodes. It should be remembered that the general expectation of life in these patients under normal conditions would not be great, and that many of them were also suffering from some other form of chronic disease, particularly cardiovascular and renal. In almost all cases there was very marked oral sepsis.

For purposes of description it has been necessary to adopt some arbitrary method of classification, and, accordingly, the primary lesions have been classed into four groups, A, B, C, and D, depending upon the extent of the primary disease. In addition, the glands of the neck have been classified into three groups, A, B, and C. The A type of primary lesions is superficial and usually of short duration, whereas the D group cases are practically hopeless. The A