Calcium Metabolism in Acromegaly

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Summary: A total of 78 acromegalic patients were studied before and after treatment by yttrium-90 needle implantation.

Among the untreated patients 16% had a borderline or raised serum calcium. In half of these patients the serum calcium fell to normal after remission of their acromegaly. In the others the hypercalcaemia was due to associated proved or probable hyperparathyroidism. A downward trend of the serum calcium was noted even in the normocalcaemic patients with remission of their disease.

Only 20% of untreated patients had a raised serum phosphate, and follow-up showed this measurement to be a poor index of disease activity.

Net calcium absorption and calcium balances in five patients in this series and 12 others from the literature were essentially normal for their given level of calcium intake. No patient showed definite radiological evidence of osteoporosis and vertebral fractures.

Bone uptake rate of calcium-47 and stable strontium was raised in the untreated state in all nine patients studied. The 24-hour strontium space was raised in 73% of untreated patients and fell to normal after treatment in all the retested patients in whom it was high initially.

Introduction

The effect of acromegaly on calcium metabolism has been of interest for a long time. Albright and Reifenstein (1948) reported that the "serum calcium and phosphatase values are normal, and the serum phosphorus level usually definitely high." Molinatti *et al.* (1961), however, found a raised serum calcium in 6 out of 13 patients, which fell to normal after treatment of the acromegaly. They also found a raised urinary calcium in their untreated patients, which similarly fell after treatment.

Many authors (Scriver and Bryan, 1935 ; Bauer and Aub, 1941 ; Albright and Reifenstein, 1948 ; Molinatti *et al.*, 1961 ; Bell and Bartter, 1967) have suggested that acromegaly is associated with osteoporosis, and have put forward various possible explanations. However, vertebral fractures have not been described in any of the reported cases, and Doyle (1967) found an essentially normal ulnar bone density and no pathological fractures in 53 acromegalic patients. Furthermore, periosteal new bone formation on the anterior surfaces of the vertebrae, with an increase in their anteroposterior diameter and increased periosteal new bone formation in the long bones, are common features of the disease (Lang and Bessler, 1961 ; Doyle, 1967).

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The present paper reports some observations on calcium metabolism in acromegalic patients before and after treatment by yttrium-90 pituitary implantation.

Methods

Patients Studied

Observations were available on 78 acromegalic patients aged 24 to 66 (mean 47) years ; 35 were male and 43 female. On their initial assessment they were assessed as having active disease on the basis of their clinical features, insulin resistance (or associated diabetes), and raised serum growth-hormone levels during an oral glucose tolerance test (>5 and usually >10 mμg./ml. for mean of one- and two-hour values: Fraser and Wright, 1968a).

All the patients were treated by pituitary implantation with yttrium-90 (Fraser and Wright, 1968b). Their overall response to implantation was graded at six months or more postoperatively into good, partial, or none. Good responders were those who showed a regression of symptoms and acromegalic facial features, as well as a return to normal insulin sensitivity or an amelioration of pre-existing diabetes. Partial responders were those who showed some but not all of these changes. Non-responders were those who showed no change at all.

Measurements

We are indebted to the Department of Chemical Pathology for these measurements, all of which were done by the methods of Wootton (1964).

(1) Serum calcium was estimated by flame spectrophotometry on samples taken fasting and without stasis, 52% of the values representing the means of two or more estimations. All of the patients with borderline (5.5 mEq/l.) or raised (>5.5 mEq/l.) values had at least two estimations done.

(2) Serum phosphate and alkaline phosphatase were estimated by the Technicon AutoAnalyzer method.

(3) The 24-hour urinary calcium was estimated by flame spectrophotometry. The samples were collected after three days on a diet containing less than 25 mEq Ca/day in about half of the patients and on an unrestricted ward diet in the others.

(4) Phosphate excretion index was done fasting as outlined by Nordin and Fraser (1960). It measures the phosphate/creatinine clearance ratio in terms of its departure from the expected ratio for the prevailing level of serum phosphate.

(5) Calcium balances were all measured by means of standard metabolic unit procedures. All patients had a five-day period of equilibration, and then a minimum of three three-day chromium-corrected (Whitby and Lang, 1960) faecal and urine pools were measured.

(6) The 24-hour strontium space, which is a measure of the exchangeable pool of calcium, was calculated as described by Fraser *et al.* (1960). Results are expressed in plasma units, the plasma volume for this purpose being taken as 5% of the body weight in kilograms.

(7) Kinetic studies were carried out with ^{47}Ca or stable strontium. Calculations of exchangeable pool size and bone uptake rate were

done with a turnover-difference method (North *et al.*, 1962). The normal range is that of Joplin *et al.* (1967).

Results

Serum Calcium

Serum calcium levels of the untreated patients are shown in Fig. 1. Twelve (16%) of them had borderline or clearly raised serum calcium levels (see Table). In the five patients with only slight rises of the serum calcium (5.5 and 5.6 mEq/l.) the post-implant values fell to clearly normal levels; thus their abnormality proved reversible by treating the acromegaly itself, and this group has been designated as "non-hyperparathyroid" in the Table. In the four with higher initial serum calcium levels, one (Case 6) showed no fall when her disease went into partial remission after pituitary implantation, and subsequently became normal after removal of a hyperplastic parathyroid gland (further details of this patient have been reported by Hartog *et al.* (1967)). One patient (Case 7) was too frail for neck exploration; one (Case 8) had a parathyroid adenoma removed shortly after implantation, with restoration of normal serum calcium; and one (Case 9), who now has a raised phosphate excretion index of +0.14, awaits further follow-up. These four cases have been designated as the "hyperparathyroid group" in the Table.

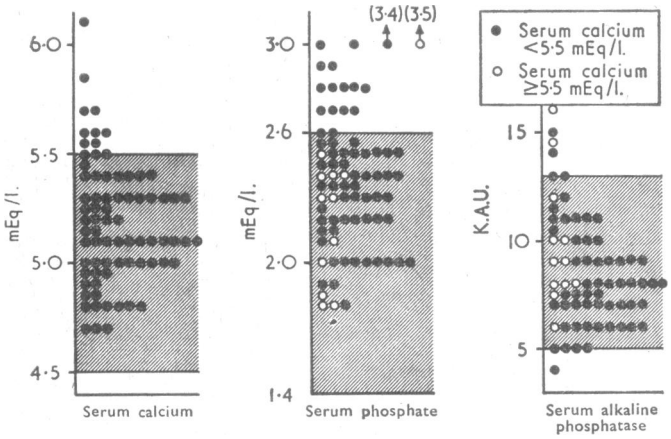

FIG. 1.—Serum calcium, phosphate, and alkaline phosphatase levels in all patients before pituitary implantation. Shaded areas indicate the normal ranges. Alkaline phosphatase fell to normal after implantation in all four patients with raised values.

Those patients who were normocalcaemic in the untreated state showed a downward trend of the serum calcium after effective treatment of the acromegaly (Fig. 2).

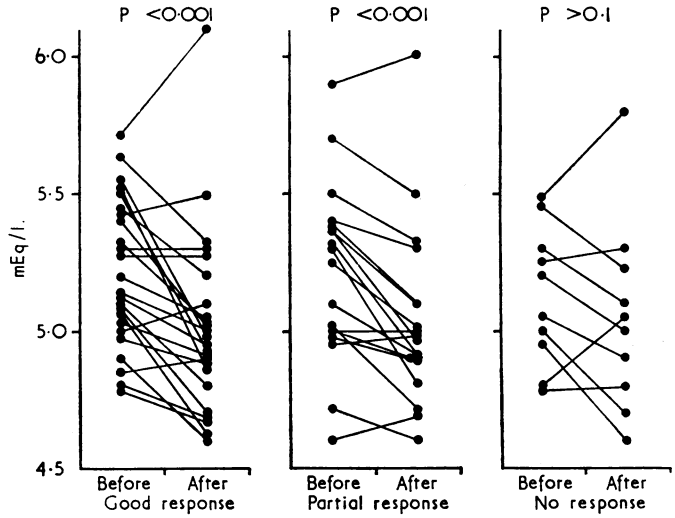

FIG. 2.—Change in serum calcium at six months or more post-implant.

Serum Phosphate

Only 15 (20%) of the untreated patients showed a raised serum phosphate, though the mean serum phosphate of the group as a whole was above the mean normal range (Fig. 1). No change was noted in the serum phosphate in the group of 41 patients who showed a remission of the acromegaly.

Urinary Calcium

The 24-hour urinary calcium was raised—that is, >15 mEq/24 hours—in 32 (47%) of the untreated patients (Fig. 3). There was no difference in urinary calcium in the dieted and non-dieted patients, the mean values being 16.0 and 16.5 mEq/day respectively. There was no correlation between the serum and urinary calcium when the whole series of 68 patients with these data was analysed. After treatment of the acromegaly there was a fall ($P<0.05$) in urinary calcium in the group of good responders but not in the partial responders (Fig. 4). Those with the highest initial values showed the greatest falls.

Details of 12 Patients with Hypercalcaemia

Case No.	Pre-implant: Serum Ca (mEq/l.)	Serum Inorg. PO_4 (mEq/l.)	Serum Alkaline Phosphatase (K.A.u.)	Urine Ca (mEq/d.)	Phosphate Excretion Index	Sr space (pl. u.)	Post-implant*: Serum Ca (mEq/l.)	Serum Inorg. PO_4 (mEq/l.)	Serum Alkaline Phosphatase (K.A.u.)	Urine Ca (mEq/d.)	Phosphate Excretion Index	Sr space (pl. u.)	General response to implant	Findings at neck exploration
Normal range:	4·5–5·5	1·4–2·6	5–13	5–15	+0·09–−0·09	<18	4·5–5·5	1·4–2·6	5–13	5–15	+0·09–−0·09	<18		
Non-hyperparathyroid Group														
1	5·6	2·3	12	17	—	—	5·3	2·0	9	16	—	—	Good	—
2	5·5	2·4	8	14	—	—	5·0	2·3	6	11	—	—	Good	—
3	5·6	2·4	16	—	—	31·6	4·9	1·9	12	11	—	13·8	Good	—
4	5·5	2·5	10	8	—	—	5·1	2·0	10	22	—	—	Good	—
5	5·5	2·4	9	10	—	18·5	5·2	2·5	8	10	−0·06	17·8	Partial	—
Hyperparathyroid Group (proved or probable)														
6	5·9	1·9	17	11	+0·10	—	6·1	1·7	13	6	+0·21	13·5	Partial	One hyperplastic gland. Two normal
7	5·7	1·8	9	12	+0·06	25·6	5·9	1·6	11	13	+0·14	12·3	Good	—
8†	6·2	2·0	6	11	—	11·9	—	—	—	—	—	—	—	Only one gland found—adenoma
9	5·7	1·8	8	23	+0·10	—	5·5	1·8	12	23	+0·14	—	Partial	—
Awaiting follow-up														
10	5·6	3·5	8	26	—	20·0	—	—	—	—	—	—	—	—
11	5·6	2·3	7	26	+0·01	20·5	—	—	—	—	—	—	—	—
12	5·6	2·4	10	25	—	23·5	—	—	—	—	—	—	—	—

* At the latest assessment made, which was at least six months post-implant. † Follow-up irrelevant because of parathyroidectomy shortly after implant.

As noted in Fig. 3 and the Table, the two patients with proved hyperparathyroidism had relatively low calcium excretions.

Phosphate Excretion Index

The phosphate clearance as measured by the phosphate excretion index was normal in the untreated state in all 9 normocalcaemic patients in whom this measurement was made (Fig. 3), but one patient (Case 6) with proved associated hyperparathyroidism and another (Case 9) with probable associated hyperparathyroidism did have slightly raised levels.

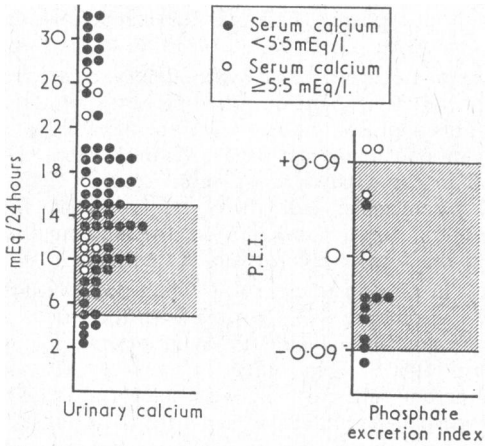

FIG. 3.—Urinary calcium and phosphate excretion index before pituitary implantation. Shaded areas indicate the normal ranges.

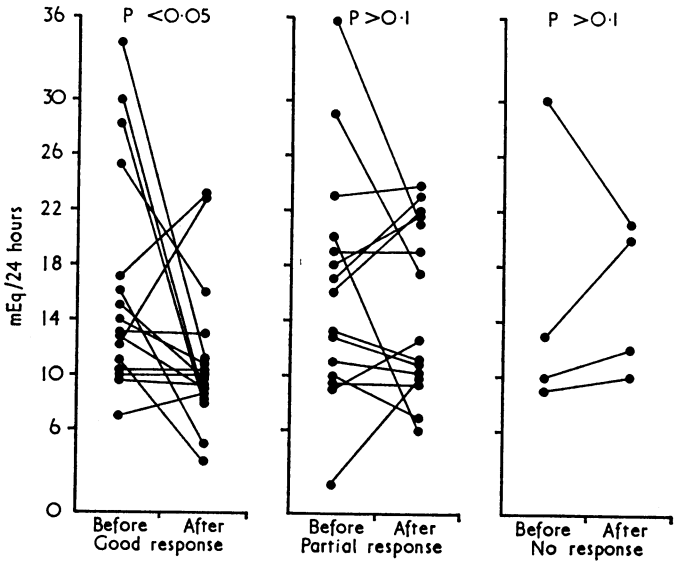

FIG. 4.—Change in urinary calcium at six months or more post-implant.

All four patients in whom the phosphate excretion index was measured both before and after implantation showed a rise in phosphaturia (Fig. 5). In one of the four (Case 7) the pre-implant phosphate excretion index was normal, but it rose above the normal range after a "good" remission of her acromegaly; as noted above, this patient also has persistence of obvious hypercalcaemia and hence probably has associated hyperparathyroidism.

24-hour Strontium Space

The 24-hour strontium space was raised in 19 (73%) of the 26 untreated patients tested (Fig. 6), and fell to normal in all retested patients in whom it was high to begin with (Fig. 7).

An attempt was made to correlate the 24-hour strontium space with the metacarpal cortical bone thickness (Joplin and Hartog, 1967) and with the ulnar bone density (Doyle, 1961), but no correlation was found. Likewise there was no correlation between the 24-hour strontium space and the serum growth-hormone levels measured during a standard glucose tolerance test.

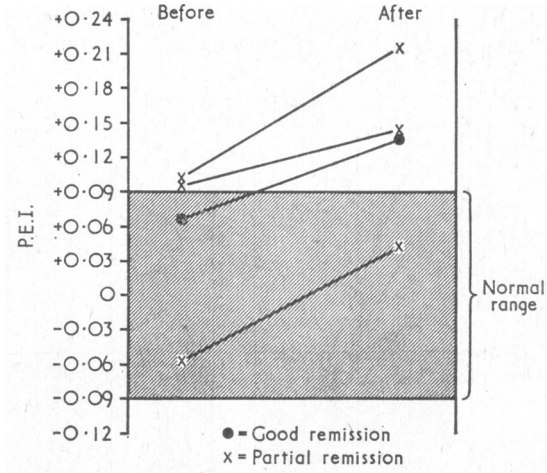

FIG. 5.—Change in phosphate excretion at six months or more post-implant.

Bone Uptake Rate of Tracers

All nine patients in whom the more sensitive full kinetic studies were done showed an increased rate of uptake of tracer into bone in the untreated state (Fig. 6). In six out of nine patients the kinetic studies were made with stable strontium,

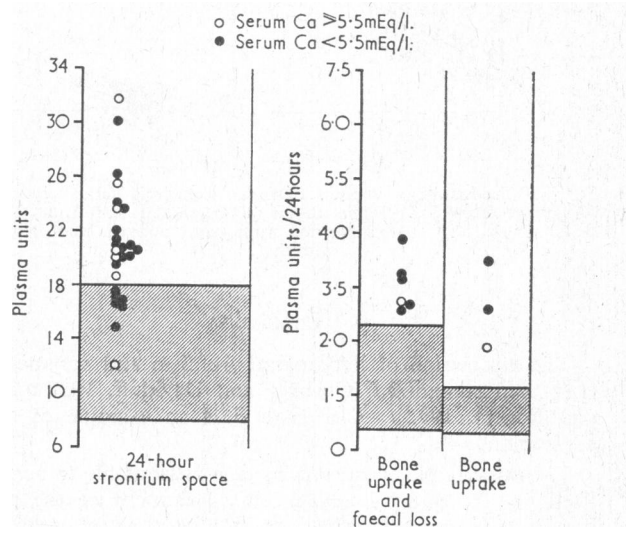

FIG. 6.—24-hour strontium space and bone uptake rate of tracer before pituitary implantation. Normal ranges are indicated by shaded areas. Stable strontium was also used for the six studies reporting "bone uptake and faecal loss," and ^{47}Ca for the other three.

and the relatively small loss of tracer into faeces was not measured separately; hence their values are plotted as "bone uptake rate plus faecal loss." In the other three patients ^{47}Ca was used, and the uptake into bone is reported.

Balance Data

Calcium balances in five of our patients and 12 others from the literature are plotted against their level of intake in Fig. 8. The normal ranges are derived from Nordin and Smith (1965).

All but one of the patients had a normal net absorption. The combined excretion of calcium in faeces and urine was normal in 11 and increased in six cases. The latter were therefore the only patients in abnormally negative calcium balance, and became so at levels of calcium intake of less than 0.35 mEq/kg./day, which is well below the national average as reported by the Ministry of Agriculture (1963). In view of their normal net calcium absorption these patients were in abnormally negative calcium balance because of their relatively high urinary calcium when maintained on a low dietary intake.

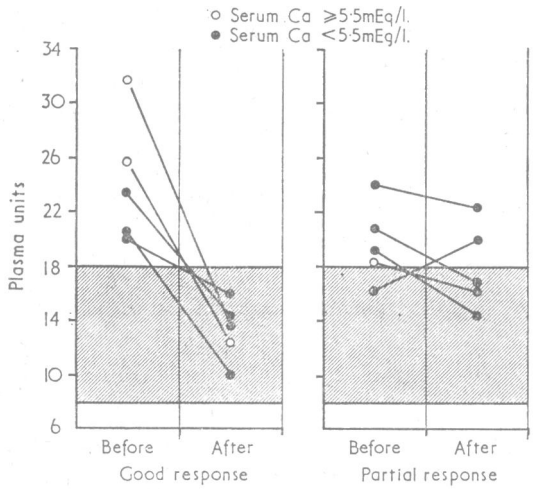

FIG. 7.—Change in 24-hour strontium space at six months or more post-implant. Normal ranges are indicated by shaded areas.

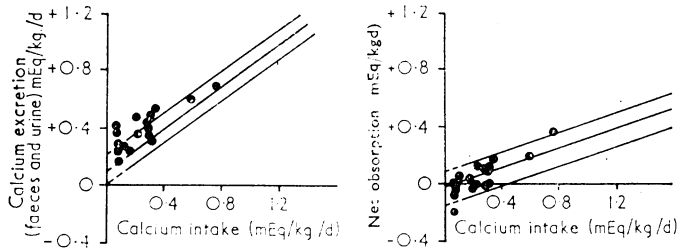

FIG. 8.—Pretreatment calcium balances from this series are combined with those from Scriver and Bryan (1935), Bauer and Aub (1941), and Bell and Bartter (1967). Normal ranges are derived from Nordin and Smith (1965).

Discussion

The association of hyperparathyroidism and acromegaly has long been recognized (Cushing and Davidoff, 1927 ; Hadfield and Rogers, 1932). Our Case 6 is an example of such an association.

The occurrence of hypercalcaemia attributable to acromegaly itself, as shown by its relief after treatment of the pituitary disease, has been described by Molinatti *et al.* (1961), who reported six cases, and by Summers *et al.* (1966), who reported one such patient. Our findings confirm the occurrence of this second variety of hypercalcaemia in acromegaly. In addition, we found a downward trend in the serum calcium of the normocalcaemic patients after effective treatment of their disease, suggesting a general tendency to a higher serum calcium level in acromegaly.

This tendency to a rise of the serum calcium in acromegaly may be due to the action of growth hormone in raising the level of plasma citrate (Henneman and Henneman, 1960), which would also account for the rise of the complexed fraction of calcium (Harnapp, 1968). However, studies of the acute effect of administered growth hormone have not shown any consistent change in the total serum calcium—for example, Henneman *et al.* (1960) and Daughaday and Parker (1965). An alternative explanation might be that growth hormone may have a parathyrotrophic action as postulated by Houssay (1936) and by Fraser and Harrison (1960), thus causing mild hypercalcaemia if maintained for a prolonged period. If such a growth-hormone-induced parathyroid hyperplasia persisted long enough the development of autonomous function would seem possible. However, it is also possible that the association of autonomous hyperparathyroidism and acromegaly is the result of a genetic abnormality as has been suggested for other types of the pluriglandular syndrome (Wermer, 1963).

Contrary to earlier reports (Albright and Reifenstein, 1948) that the serum phosphate is a useful index of acromegalic activity, we found that only 20% of untreated patients had a raised serum phosphate. This is in agreement with the findings of Molinatti *et al.* (1961) and of Gordon *et al.* (1962).

The common occurrence of hypercalciuria in acromegaly and its value in the assessment of the response to treatment is confirmed. This is probably due both to the direct effect of growth hormone in enhancing calciuria (Medical Research Council, 1959) and to the slightly raised mean serum calcium level in untreated acromegalics. As there was no correlation between the serum and urinary calcium in the untreated state it is likely that the former mechanism is dominant.

The rise in phosphate clearance which occurred after remission of the acromegaly is in keeping with the observed effect of growth hormone in reducing the renal clearance of phosphate (Gershberg, 1960). This effect of growth hormone in an untreated acromegalic may mask the usual increased phosphaturia of hyperparathyroidism in a patient with both diseases.

The net absorption of calcium was essentially normal in data from our own patients and from those reported in the literature. Calcium balance was also normal except at low dietary calcium intakes of less than 0.35 mEq/kg./day, when 6 out of 16 patients went into abnormally negative calcium balance because of a high urinary calcium. It is this high urinary calcium which may have led previous authors (Scriver and Bryan, 1935 ; Bauer and Aub, 1941 ; Albright and Reifenstein, 1948 ; Bell and Bartter, 1967) to associate a negative calcium balance with acromegaly. Their studies were done on low intakes of calcium and their results were cited without reference to a normal range for such levels of intake. The same authors also refer to the occurrence of osteoporosis in acromegaly, but full radiological assessment of the patients in the present series did not show any with vertebral or other pathological fractures. It is possible that the absence of osteoporosis in this series might be due to the relative youth of our patients (mean age 47 years), but, even taking this into consideration, it seems unlikely that osteoporosis is any more common in acromegaly than in the general population.

The bone uptake of tracer was increased in all nine patients studied, and the exchangeable pool of calcium as measured by the simple 24-hour strontium space was raised in 73%. An increased bone uptake rate of tracer in acromegaly has also been reported by Eisenberg and Gordan (1961), who studied eight cases, and by Bell and Bartter (1967), who studied four cases. Our finding of an increase in the exchangeable pool of calcium is in agreement with the studies of Eisenberg and Gordan (1961) and of Haymovitz and Horwith (1964). Bell and Bartter (1967), however, found a normal exchangeable pool in their four cases, but they do make the point that the acromegaly was not highly active in any of their patients, and, furthermore, that one of them also had hypothyroidism secondary to pituitary hypofunction. After effective treatment of the acromegaly the 24-hour strontium space fell to normal, and this would appear to be a simple useful additional measurement in the assessment of the response to treatment in acromegaly.

We wish to acknowledge our indebtedness to the staff of the Department of Chemical Pathology, and the Metabolic Unit Laboratory for the estimations of calcium and phosphate and balance

data ; to the house staff, sisters, and nurses ; to the many consultants and general practitioners who referred patients ; and to the patients themselves for their co-operation in the metabolic studies. One of us (A. N.) is in receipt of a Commonwealth Scholarship, United Kingdom award and another (N. T.) is supported by a W.H.O. Fellowship.

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Outbreak of Food-poisoning Caused by Salmonella virchow in Spit-roasted Chicken

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Summary : Salmonella virchow food-poisoning acquired from eating chicken caused illness in at least 50 people who attended a tennis club function in Liverpool, and in many other people in the Merseyside area. In some cases the illness was severe, with positive blood cultures, and 35 people were admitted to hospital.

The source of infection was a retail shop which received deep-frozen chickens already contaminated with S. virchow from a packing-station in Cheshire. These chickens were spit-roasted after inadequate thawing and subsequently handled under unhygienic conditions. The result was a massive build-up of salmonella contamination in the shop and in the chicken portions sold.

S. virchow was isolated from over 160 patients and contacts in the Merseyside area during the outbreak and many continued to excrete the organism in the faeces after four months. Antibiotic treatment was not recommended because there was no evidence that it shortened the duration of excretion.

A high rate of contamination of chickens from a packing-station by a salmonella type capable of causing serious disease in man is clearly a public health problem which cannot be ignored.

The use of rotary spits for roasting chickens requires thorough investigation and appraisal, because as operated at present they evidently constitute a public health hazard.

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Introduction

Salmonella infection of chickens dressed in broiler packing-stations has been the subject of recent reports from Britain (Dixon and Pooley, 1961), Canada (Magwood *et al.*, 1967), and U.S.A. (Wilson *et al.*, 1961) ; Woodburn, 1964 ; Wilder and MacCready, 1966). This represents a serious public health hazard because the salmonellae may be present not only on the surface but also in the deep tissues of the chickens, and if these organisms are to be destroyed in the cooking process this must be such as to ensure adequate penetration of heat to the interior of the bird. We describe here an outbreak of food-poisoning by *Salmonella virchow* which occurred because infected chicken carcasses were sent from a packing-station to a retail establishment where they were inadequately cooked on a spit-roaster and handled under unhygienic conditions. This led to an overwhelming build-up of salmonella contamination of the premises.

The Outbreak

As a result of a telephone call on 3 July 1968 from a general practitioner about a possible outbreak of food-poisoning, immediate investigation showed that many persons had been affected, some requiring admission to hospital, among those who had attended a tournament at a suburban tennis club on Saturday 29 June.

The food served at the club consisted of quarters of spit-roasted chicken, salad, cakes, fruit jelly, and ice-cream. Epidemiological inquiries quickly established that all the affected persons had eaten the chicken, most of them at about 5 p.m. ; some remaining portions of chicken were eaten at about 10 p.m.,