to stimuli of many kinds. Other toxins seem to block processes concerned in the transmission of co-ordinating stimuli between groups of cells. This appears to be the case with the tetanus and botulinum toxins, which interfere seriously with the acetylcholine mechanism (Ambache *et al.*, 1948a, 1948b; Burgen *et al.*, 1949). In other instances, especially with the endotoxins now being disentangled from Gram-negative bacteria, cellular metabolic functions seem to be the foci of attack, but there is an appalling lack of information about these matters. Clearly we are on the threshold of a vast new world of cellular research from which we may gain rich treasure if we explore it critically and with imagination. The reward will include, I feel sure, progress not only in fundamental knowledge about life but in applied pathology, carrying with it new ideas about the recognition and treatment of disease no less than the forestalling of sickness.

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According to a report of an informal working party on the treatment and disposal of sewage sludge (H.M.S.O., 1954, price 2s. 6d. net), the efficient treatment and disposal of sewage sludges, together with the production of useful and valuable by-products, constitute the most difficult and costly work undertaken at sewage works. The report discusses five methods of disposing of sewage sludge. These are in the order in which they should generally be given consideration: (1) Disposal in a liquid state, preferably after digestion, as a method of manuring grasslands. (2) Disposal in a liquid state, preferably after digestion, to manure agricultural land for general purposes. (3) Failing the possibility of final disposal in liquid form, efforts should be made to obtain an end-product in some dry state suitable, preferably after maturing and pulverization, to form slow-acting manure for agricultural land. (4) A still drier product than the above can be made, but this entails the use of expensive equipment. (5) Favourable conditions, usually to be found in rural areas and small market towns, may exist for the method of disposing of liquid sludge by composting with other waste materials, generally separated from household refuse,

POTASSIUM-LOSING NEPHRITIS PRESENTING AS A CASE OF PERIODIC PARALYSIS

BY

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Recent workers (Platt, 1950; Nickel *et al.*, 1953) have emphasized a tendency to urinary loss of electrolyte in renal failure in addition to the more familiar excess retention of end products of nitrogen metabolism. In some patients this electrolyte loss dominates the clinical picture, and in the last 10 years cases of both sodium and potassium deficiency as a result of renal disease have been reported. The type characterized by excess sodium loss was first described by Thorn *et al.* (1944) under the name of "salt-losing nephritis." Such cases have many features like Addison's disease, in that weight loss, hypotension, cachexia, and low serum sodium are present, often associated with some pigmentation of the skin. They differ in that there is no favourable response to deoxycortone or to cortisone, but only to liberal supplements of sodium chloride.

Potassium loss often does not produce such obvious clinical effects, and there is little doubt that many cases of potassium deficiency due to excess urinary loss have passed unrecognized. Brown *et al.* (1944) first described cases of periodic attacks of hypokalaemic paralysis or weakness as a result of renal tubular acidosis. More recently, hypokalaemic paralysis has been described in the de-Toni-Fanconi syndrome, of both the adult and the infantile types (Milne *et al.*, 1952; Bickel *et al.*, 1953). In this paper we describe metabolic studies of a case of chronic pyelonephritis with severe urinary potassium loss.

Case Report

The patient was a married negress aged 41. She had lived in Nigeria until 1953, when, during a visit to Great Britain, her illness was first diagnosed and treated. She had been in good health until 1944, when she suddenly felt her legs becoming heavy and weak. There was complete paralysis of the legs and soon afterwards of the arms, lasting for two weeks. Since then she has suffered from periodic attacks of weakness of the limbs lasting from 2 to 20 days before relief occurs. There has never been any paralysis of the muscles of deglutition, respiration, or phonation, nor any diplopia. The attacks come on about every three months and tend to be precipitated by exposure to cold. She has always felt reasonably well between the attacks, but there is usually some slight residual muscular weakness. Her last attack started whilst on air passage to Great Britain. She was admitted to another hospital in this country with complete paralysis of the legs and weakness of the arms. A diagnosis of hypokalaemic paralysis of unusual type was made, and she was transferred to Hammersmith Hospital for further study.

On inquiry it was found that she had had three episodes of dysuria and frequency of micturition associated with pyrexia in 1945, 1946, and 1947. For the last three years there had been polyuria with nocturnal frequency of micturition. There was no family history of any similar urinary or paralytic symptoms.

The patient was co-operative and healthy-looking. On first admission to hospital she was unable to move her legs

and the tendon reflexes were absent. There was considerable weakness of the arms, but she was able to move them, and the tendon reflexes were present. There was no impairment of sensation.

She was hypertensive (blood pressure 180/110), and there was slight cardiac enlargement with an apical presystolic triple rhythm. Chest radiographs revealed no pulmonary abnormality. Intravenous pyelography showed a defective concentration of the contrast medium, but no evidence of renal calculus, nephrocalcinosis, or hydronephrosis. The electrocardiogram (Fig. 1) showed changes typical of hypokalaemia.

FIG. 1.—Electrocardiogram (lead V_5) before (left) and after potassium supplements.

There was depression of the S-T segment, inversion of the T wave, and an upright U wave in the left precordial leads. After potassium supplements had been given for several days these abnormalities were still present, but reduced in degree. There had also

been a considerable reduction of voltage of the QRS complex in all leads, a change which has been described by Bryant (1948) after the administration of potassium salts.

The urine showed a constant albuminuria (2 g./l. Esbach). There was complete isosthenuria, specific gravity being fixed at 1011 despite fluid restriction. A catheter specimen of urine showed occasional erythrocytes and pus cells, but was sterile on culture. Blood urea ranged from 27 to 42 mg./100 ml. Urea clearance was 58 ml./minute, and endogenous creatinine clearance 65 ml./minute. The patient was unwilling to permit determination of inulin and para-amino hippurate clearances, but it is probable, from endogenous creatinine clearance figures, that her glomerular filtration rate was approximately 50% of normal.

Serum electrolyte values before and during treatment are given in Table I. There was no evidence of renal osteodystrophy, serum calcium was 9.0 mg./100 ml., serum in-

acid by the distal tubular cells and that the particular tubular defect was not due to absence of renal carbonic anhydrase.

The diagnosis was clearly one of hypokalaemic periodic paralysis. Balance data showed a constant abnormal loss of potassium in the urine, and therefore a diagnosis of familial periodic paralysis could be excluded. Cushing's syndrome, which causes increased urinary potassium loss, could be excluded on clinical grounds. In addition, the plasma level of 17-hydroxycorticosteroids determined by the method of Bayliss and Steinbeck (1953) was normal, and chromatographic analysis of compounds E (cortisone) and F (hydrocortisone) in the urine by the method of Cope

FIG. 2.—Electrolyte balance of case of potassium-losing nephritis during 26 days as an in-patient. Intake is plotted downwards from the baseline. Negative balance is recorded by the distance of each column above the base-line, and positive balance below this line. Black columns represent faecal excretion and open columns urinary excretion. Faecal sodium and chloride were negligible.

TABLE I.—Serum Electrolyte Values During Treatment of a Case of Potassium-losing Nephritis

Date	Sodium mEq/l.	Potassium mEq/l.	Chloride mEq/l.	Bicarbonate mEq/l.
In-patient:				
24/10/53	145	1.4	87	47
26/10/53	145	1.5	95	34
30/10/53	143	2.7	105	30
3/11/53	140	2.8	104	31
11/11/53	140	2.7	104	29
19/11/53	140	2.9	104	29
Out-patient:				
7/12/53 to 22/3/54	145	3.3	100	30.5
Mean value	140-152	2.6-4.1	92-106	25-35
Range				

Potassium supplements were started on 27/10/53.

organic phosphorus 3.4 mg./100 ml., and serum alkaline phosphatase 3.8 King-Armstrong units per 100 ml. Serum albumin was 2.9 g./100 ml. and serum globulin 4.8 g./100 ml. (electrophoretic values). The high globulin was due to increase of the beta- and gamma-globulin fractions. There was no evidence of steatorrhoea, over 97% of ingested fat being absorbed.

The urine was normally either slightly alkaline or neutral in reaction. After ingestion of 12 g. ammonium chloride in six hours the minimum urinary pH was 6.6, showing an inability to secrete an acid urine despite an adequate acidifying stimulus. A rapid rise of urinary pH to a maximal value of 8.0 occurred after the ingestion of 250 mg. of a carbonic anhydrase inhibitor ("diamox"), showing that there was some synthesis of hydrogen ion from carbonic

FIG. 3.—Cumulative balances of potassium, sodium, and chloride during the treatment of a case of potassium-losing nephritis with potassium supplements.

and Hurlock (1945) gave normal results. Bio-assay of electrocortin excretion by Cope and Garcia-Llaurado (1954), however, gave abnormally high figures. In view of the history and findings suggestive of chronic pyelonephritis it was thought that renal tubular damage was the cause of the hypokalaemia.

Balance Data.—The patient was put on a fixed standard diet containing 85 mEq of potassium and 140 mEq of sodium daily. Standard metabolic balance and analytical methods were used.

After a two-day preliminary period without potassium supplements, the patient was given 5 g. potassium chloride in water three times daily (200 mEq/day). In six days the patient retained almost 800 mEq of potassium and simultaneously lost over 500 mEq of sodium (Figs. 2 and 3). There was also a positive balance of chloride of more than 400 mEq. There was therefore excess retention of acidic over basic radicals with correction of the hypokalaemic alkalosis. On stopping the potassium supplements on days 9 and 10 the patient went into severe negative potassium balance, losing over 100 mEq potassium per day, despite the fact that the serum potassium had only risen to 2.8 mEq/l. and the electrocardiogram still showed unequivocal evidence of hypokalaemia. This confirmed that the potassium deficiency was due to grossly excessive urinary loss. The potassium clearance was now almost as high as that of endogenous creatinine, being 54 ml./minute, with ratio $C_k/C_{cr}=0.83$.

It now seemed undesirable to continue potassium supplements with this large dose of potassium chloride. The hypokalaemic alkalosis had been fully corrected before the potassium deficit had been completely restored. Continued dosage with pure potassium chloride would have caused a frank acidosis. A further complication arose from the isosthenuria. In Fig. 4 we show the relationship between the daily excreted osmotic load of solute and the daily urinary volume. The large dose of potassium chloride increased the urinary solute excretion from 800 to 1,375 m.osm. per day, with a consequent rise of urinary volume from 2 to 4.6 litres daily. The patient was therefore stabilized on a lower dosage of potassium salts, given as a mixture of 2 g. potassium chloride and 1 g. potassium citrate three times daily. On this regime the patient remained in slight positive potassium balance during the remainder of her stay in hospital, and the cumulative gain eventually exceeded 1,000 mEq of potassium (Fig. 3). There was no further gain or loss of sodium, but some excess chloride retained during the previous high chloride regime was gradually eliminated. There was no gain or loss of

FIG. 4.—Relationship between the daily solute excretion and the daily urinary volume in the case of potassium-losing nephritis.

calcium or magnesium throughout, but during the period of maximal potassium retention a positive balance of 400 mg. of phosphorus occurred.

A control balance of 12 days' duration was observed in a normal subject (M.D.M.). After a three-day basal period, potassium chloride at a dosage of 15 g. (200 mEq) per day was taken in addition to a constant diet for six days. A three-day recovery period without added potassium salts was included (Fig. 5). The normal kidney was found to preserve almost perfect homeostasis, very little biochemical change occurring. In Table II we compare the effects of six days on this high dosage of potassium chloride in the potassium-depleted patient and in the normal control.

The patient was discharged from hospital in a state of moderate hypokalaemia with serum potassium averaging 2.8 mEq/l. The serum bicarbonate was within normal limits, and the average daily urinary volume was about 3,000 ml. Her muscular strength had much improved and the tendon reflexes of the legs were just present on reinforcement. The apical presystolic triple rhythm was no longer present.

FIG. 5.—Electrolyte balance in a normal control subject. The presentation is similar to Fig. 2. From the fourth to the ninth day inclusive, 15 g. of potassium chloride was taken in addition to a standard fixed diet.

TABLE II.—Comparison of Biochemical Changes Induced by Daily Supplements of 15 g. Potassium Chloride in a Case of Potassium-losing Nephritis and a Normal Control Subject

	Potassium-losing Nephritis	Normal Control
Serum potassium { Before K ..	1.5 mEq/L.	4.0 mEq/L.
After K ..	2.8 "	4.4 "
Serum bicarbonate { Before K ..	47 "	28 "
After K ..	30 "	28 "
Serum chloride { Before K ..	87 "	105 "
After K ..	105 "	107 "
Clearance ratio { Before K ..	27%	8.5%
(C _k /C _{cr}) After K ..	83%	47%
Cumulative potassium balance ..	+796 mEq	+15 mEq
Cumulative sodium balance ..	-528 "	-125 "
Cumulative chloride balance ..	+446 "	+47 "
Cumulative phosphate balance ..	+5.5 m.mol.	+18 m.mol.

She has remained reasonably well during a period of four months' out-patient observation. There have been no further attacks of periodic paralysis, although some muscular weakness has sometimes been present. Supplements of 6 g. potassium chloride and 3 g. potassium citrate daily have in general been sufficient, but the dose has had to be increased for short periods when muscular weakness or hypokalaemia occurred. Serum electrolyte values during this period are summarized in Table I.

Discussion

The great majority of cases of excessive electrolyte loss in renal disease are secondary to chronic atrophic pyelonephritis. Evidence for this in relation to "salt-losing

nephritis" is discussed by Enticknap (1952). This case is probably one of the least complicated and most severe examples of potassium loss from pyelonephritis yet described. The balance data show that the total potassium deficit must have been greater than 1,000 mEq. Even after the patient had retained this amount of potassium there was unequivocal evidence of residual deficiency in that the serum potassium was still only 2.8 mEq/l., and the electrocardiogram showed the changes of hypokalaemia. In experimental potassium depletion (Black and Milne, 1952; Evans *et al.*, 1954), with deficiencies of about 300 mEq, the serum potassium level is of the order of 3.2 mEq/l. and any electrocardiographic change is slight and equivocal. It is likely, therefore, that the original total deficit of potassium in this patient was of the order of 1,500 mEq, which is just over 40% of her expected total body content of potassium. The balance data show that most of the intracellular potassium deficit had been replaced by a large increase of intracellular sodium. Approximately 70% potassium was replaced by sodium: this agrees well with the results obtained by Cooke *et al.* (1952) in potassium depletion in rats. The remainder of the potassium deficit is balanced by transfer of hydrogen ion from the extracellular to the intracellular phase, thus explaining the severe extracellular alkalosis found in this patient. Most of the retained chloride can be accounted for by the correction of this alkalosis. A positive phosphorus balance is almost invariable during the restoration of a potassium deficit. In this patient it was very small, and amounted to only 10 m.mols. of phosphate.

It is remarkable that this extreme degree of potassium deficiency should have caused such relatively mild symptoms. In the intervals between attacks of hypokalaemic paralysis this patient walked about normally and could undertake a full day's work. There was undoubtedly, however, great subjective and objective improvement in muscular power and in a general sense of well-being after partial restoration of the potassium deficit. Black and Milne (1952) have suggested that hypokalaemia associated with extracellular alkalosis causes less incapacity than a similar degree of potassium deficiency complicated by acidosis. Fourman (1954) considers that intracellular replacement of potassium by sodium may mitigate the effects of deficiency. This case seems to support these opinions. Also, potassium deficiency which has developed slowly over many years, as in this case, may probably be better compensated than the acute deficiencies seen after loss of gastro-intestinal secretions or in diabetic coma.

Usually, cases of potassium-losing nephritis are associated with acidosis either with or without renal rickets or osteomalacia (Brown *et al.*, 1944; Albright *et al.*, 1946; Milne *et al.*, 1952). Symptoms of hypokalaemic paralysis or weakness may then occur with less potassium deficit, and comparatively small supplements of potassium citrate are necessary in treatment. Only three cases similar to the one described here have been found in the literature. Earle *et al.* (1951) have described a patient with hypokalaemia from renal disease in whom the serum bicarbonate was normal, and the balance data suggest that there was a similar deficit of about 1,500 mEq of potassium. Unlike our patient, there was some tendency to a coincident sodium-losing state. Corcoran (1953) has briefly described an example of potassium-losing pyelonephritis with a normal glomerular filtration rate and with a potassium clearance almost equal to that of inulin. Wyngaarden *et al.* (1954) record a case with a similar renal lesion in which the potassium deficit was not so extreme but with a comparable degree of hypokalaemic alkalosis.

In general, there are two opposing factors which may influence the serum bicarbonate in renal tubular failure. The familial acidosis of renal insufficiency lowers the serum bicarbonate, whilst abnormal loss of potassium tends to raise it owing to the development of hypokalaemic alkalosis. In the rare cases with extreme potassium loss, serum bicarbonate may be normal or considerably raised. Inability to form a normally acid urine in response to an adequate

ammonium chloride load is more reliable proof of renal tubular acidosis than determination of serum bicarbonate, which may be influenced by a complicating potassium deficiency.

Explanation of the differential functional effects of chronic pyelonephritis can, in the present state of knowledge, only be speculative. Potassium loss in renal tubular acidosis has been claimed to be a part of the general loss of fixed base by a kidney denied the important base-conserving mechanism of ammonia synthesis (Albright *et al.*, 1946). This cannot be the explanation in this case, in which extreme potassium loss continued despite an alkaline urine and extracellular alkalosis when ammonia synthesis should be minimal. It is now considered that the most important renal mechanism for potassium excretion is a process of ionic exchange for sodium in the distal tubule (Berliner *et al.*, 1951). If this is accepted in the present case—and the very high C_k / C_{cr} clearance ratio makes such a mechanism likely—one is faced with the paradox that a destructive process has stimulated rather than depressed a normal urinary function. Selective inhibition or destruction of tubular enzyme systems will probably prove to be the reason for the diverse functional effects of pyelonephritis, and careful studies by histochemical techniques should be made if a similar case should come to necropsy. The tubular defect in this case was not due to absence of renal carbonic anhydrase, since inhibition of this enzyme resulted in a normal response.

The Differential Diagnosis of Periodic Paralysis

Periodic hypokalaemic paralysis secondary to renal disease is now easily distinguished from familial periodic paralysis in which there is no renal lesion. Points which are against a diagnosis of familial periodic paralysis in any given case are as follows:

(a) Lack of Family History.—Familial periodic paralysis is due to a dominant and usually non-lethal gene, which does not interfere with reproductive fitness. The mutation rate of this gene must therefore be low (Haldane, 1935), and thus at least 80% of true cases of the disease give a positive family history.

(b) Late Age of Onset.—At least 60% of cases of true familial periodic paralysis start below the age of 16, while potassium-losing nephritis more often occurs in a later age group.

(c) Hypokalaemia and muscular weakness should not persist between the attacks of frank paralysis in familial periodic palsy, but usually do in potassium-losing nephritis. The interpretation of serum potassium levels should, however, always be made in relation to the serum bicarbonate. Acidosis tends to cause a higher serum potassium and most nephritic cases are acidotic.

(d) The attacks tend to be of longer duration and are more severe in potassium-losing nephritis. In familial periodic paralysis the longest duration of an attack with eventual recovery is that of a case described by MacLachlan (1932) in which paralysis on one occasion lasted for eight days. The case mortality from respiratory paralysis in the familial disease is given as 10% (Talbot, 1941). The true figure is probably lower than this, since some of the fatal cases have in fact been nephritic cases, incorrectly diagnosed as sporadic examples of familial periodic palsy.

(e) A diagnosis of familial periodic paralysis should be suspect if there is clear evidence of organic renal disease. Absence of albuminuria is not a sufficient criterion, since a normal result may be obtained in some cases of chronic pyelonephritis or the Fanconi syndrome. More delicate tests of tubular function such as the urine concentration test or the ability to acidify the urine should be included.

Accuracy of diagnosis is of more than academic importance. Larger potassium supplements may be necessary in the nephritic cases and the prognosis is more grave than that of the familial disease. Correct advice with regard to the hereditary aspects of a case of periodic palsy depends on diagnostic accuracy. Mistaken diagnoses are now uncommon, but were frequent before the metabolic cause of periodic paralysis was established by Aitken *et al.* (1937).

The following cases published as sporadic examples of familial periodic paralysis are thought, on the above criteria, more likely to have been cases of potassium-losing nephritis:

Maclaire (1925); Shinosaki (1926), one case; Vernon (1936); Poulsen (1938); Smith (1939)—first case.

Summary

A case is described of chronic pyelonephritis in which urinary potassium loss resulting in periodic hypokalaemic paralysis dominated the clinical picture. It was estimated by balance data that there was a deficiency of about 1,500 mEq of potassium, amounting to 40% of the total normal body potassium. The differential diagnosis between hypokalaemic paralysis of the familial type and that secondary to a renal defect is discussed. No explanation is given for the differential effects of chronic pyelonephritis on renal tubular function.

Thanks are expressed to Dr. R. J. Porter, who first diagnosed the case and arranged transfer to Hammersmith Hospital for balance studies; and to Dr. A. G. Macgregor for the out-patient data. We are indebted to Dr. R. I. S. Bayliss for determination of plasma 17-hydroxycorticosteroids and to Dr. C. L. Cope for determination of compounds E and F in the urine. Mrs. Walwyn-Jones and her staff gave invaluable assistance in supervising the various fixed diets in the balance studies.

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The Library of Congress has just published *Scientific and Technical Serial Publications, United States, 1950-1953*. This bibliography, which covers medical journals and reports, is divided into two sections, dealing respectively with non-government and government publications. Entries are grouped under a subject classification, and an alphabetic index of subject headings is included. Information is given regarding recent changes of titles, publisher, date of first issue, and frequency. The nature of the material included in each journal is indicated (for example, original research, review literature, abstracts, etc.). This work, which should be a useful addition to scientific bibliography, was prepared under the sponsorship of the National Scientific Foundation and can be obtained from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C., price \$1.25.

SIMILARITY OF SYMPTOMATOLOGY OF PREMENSTRUAL SYNDROME AND TOXAEMIA OF PREGNANCY AND THEIR RESPONSE TO PROGESTERONE*

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An investigation was undertaken to ascertain the incidence of premenstrual syndrome in those who had previously suffered from toxæmia of pregnancy. This followed on the finding by Greene and Dalton (1953) of the high incidence of toxæmia of pregnancy (19%) among sufferers of premenstrual syndrome. The study of both diseases revealed a striking similarity of symptoms and signs suggesting a common aetiology. The successful treatment of premenstrual syndrome with progesterone (Gray, 1941; Puech, 1942; Albeaux-Fernet and Loublie, 1946; Greene and Dalton, 1953; and Rees, 1953a) suggested a possible treatment for toxæmia of pregnancy.

The investigation was carried out on 952 women, of whom 237 had suffered from toxæmia of pregnancy. Of these toxæmic mothers 40 were in the partnership practice and the remainder had been under the care of the local authority clinics, whose records were examined for the years 1942-53. Controls were women at a local engineering factory (614), and mothers with children under 5 years attending a routine infant welfare clinic (101). All were interviewed personally by me and set questions were asked. Those not already under treatment for premenstrual syndrome were given a special calendar on which to record the dates of menstruation and any recurrent symptoms during the six weeks immediately following the interview.

Premenstrual syndrome is often difficult to diagnose, for its recognition depends both on the intelligence of the patient and the severity of symptoms, so diagnosis was limited to those whose symptoms fulfilled the following conditions: (1) present in each of the three previous cycles, (2) severity sufficient to demand relief with analgesics or the seeking of medical advice, (3) occurrence at a specific phase of the menstrual cycle, confirmed by calendar and limited to the three premenstrual days, the period of menstruation, or mid-cycle. The diagnosis of toxæmia was limited to those who gave evidence of a blood pressure of 120/70 mm. Hg or below early in pregnancy, which rose after the 28th week to 140/90 mm. Hg or above, and for which treatment was instituted. Thirty-one cases of toxæmia of pregnancy were excluded owing to uncertain diagnosis or complicating factors—for example, pyelitis, placenta praevia; 96 women with no menstrual loss in the three previous months were excluded.

Results of Investigation

The results (Figs. 1 and 2) show the very high incidence of premenstrual syndrome in toxæmic mothers (86.4%), compared with controls (26.6%), and also show that the incidence of premenstrual syndrome increases in toxæmic mothers from 76.6% after one pregnancy to 100% after four pregnancies. Age had no apparent significance on the incidence.

The time of onset of premenstrual syndrome in toxæmic mothers was stated to be: puberty, 23%; following child-

*The Charles Oliver Hawthorne Prize essay, 1954.