adrenals. They become swollen and deep red. On section extensive haemorrhages may be found. The cells are pale and swollen, and are in a process of hydropic degeneration. While it is now generally supposed that the absorption of toxins from the injured skin (histamine shock) is the prime factor in the fatal outcome, the marked pathological changes found in the adrenal cortices suggest that acute cortico-adrenal insufficiency (secondary to the above-mentioned pathological changes in the cortex) plays a prominent part in these deaths. It is quite within the bounds of reason to expect that the generous administration of cortin in such cases would prevent an otherwise inevitable fatality.

Summary

In summary may I recall to you that we have briefly reviewed the probable functions of the adrenal cortex (it being the "vital" part of the adrenal gland), and have suggested the use of a potent cortical extract in certain clinical entities, including the so-called "thymic syndrome," cyclic vomiting, certain cases of infantile diarrhoea, the vomiting of pregnancy, severe infections, and severe burns. May I suggest in conclusion that it is only by applying clinically the findings of the experimental physiologist that real progress can be made in the solution of our medical problems. Such experimental clinical research can readily be made compatible with the best interests of the patient.

**** An account of the discussion on this paper will be found at page 1221.**

[Figs. 1 and 2 are reproduced from *The Adrenals*, by A. Grollman (The Williams and Wilkins Company, Baltimore, 1936).]

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A congress of the International Union for the Study of Population Problems will be held in Paris from July 28 to 31 under the presidency of Professor Adolphe Landry. A large number of papers will be read upon a diversity of populational, biometric, and demographic subjects. A 50 per cent. reduction on the French railways to and from Paris will be accorded to members attending and their families, with free entrance to the Paris Exhibition during the Congress. The British National Committee of the Union is the British Population Society, founded in 1928 to develop in Great Britain and Northern Ireland scientific studies pertaining to problems of population. Membership of this society is open to all those whose scientific or other special qualification will enable them to forward the objects of the society, and carries with it membership of the International Population Union with the right to attend and speak at meetings of the Union and to contribute papers upon populational subjects. Associate membership is open to all interested in populational problems, and includes the right to attend the International Congress. The official journal of the Union is *Population*. Full particulars of the British Population Society may be obtained from the hon. secretary, Dr. C. Conyers Morrell, D.P.H., Mudeford House, Mudeford, Christchurch, Hants.

CHRONIC AGRANULOCYTOSIS SUCCESSFULLY TREATED WITH LIVER

BY

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A pastrycook aged 25 was admitted to St. Bartholomew's Hospital on May 22, 1936, for dimness of vision. He was quite well and healthy, with normal eyesight, till five years before, when his eyes became inflamed and his vision impaired. He was partially relieved of symptoms for the time being by hospital treatment, but attacks recurred and alternated with intervals of relief. Both eyes were affected by chronic iridocyclitis, of which investigation failed to reveal the cause. In the course of these investigations he was found to have a very low white blood count. It was naturally wondered whether the leucopenia was in any way connected with the iridocyclitis, its origin or its treatment, and whether restoration of the white count to normal would improve the condition of the eyes.

Case History

Apart from the iridocyclitis the only abnormality was a shallow ulcer on the inner aspect of the cheek. The ulcer was first noticed by the patient about nine months before, and it appeared and disappeared at irregular intervals without any treatment. The family and personal history were good, and there was no history of allergy in the patient or his relatives. Nine months ago he took a proprietary tonic which then contained amidopyrine, of which he probably had some 30 grains in all. About the same time he had one or more injections of gold for the eyes without any benefit.

The blood count on May 20, 1936, was: red cells, 6,140,000 per c.mm.; haemoglobin, 102 per cent.; platelets, 250,000; white cells, 3,600, of which 1,188 were polymorphonuclear cells. Two days later the white blood count was 2,800, of which 812 were polymorphonuclear cells. The differential count on the bone marrow obtained by sternal puncture on June 4, 1936, was as follows:

Myeloblasts	3%	Eosinophils	2%
Premyelocytes	3%	Lymphocytes	4%
Myelocytes	32%	Monocytes	0.5%
Metamyelocytes	10%	Reticulum cells	0.5%
Staff neutrophils	13%	Macroblasts	11%
Segmented neutrophils	1%	Erythroblasts	20%
Basophils	0%		

The most notable feature of the marrow smear is the excessive proportion of myelocytes, apparently due to a failure in their development into polymorphonuclear cells. Maturation has been arrested, though at a later stage than in a previous case, in which the cells had not advanced beyond the myeloblast level (Witts, 1936). The myeloid cells, especially the myelocytes, seemed more fragile and more easily "smudged" than in health; their granulation was scanty and often lacked uniformity. The nucleated red cells were less mature than in the normal marrow smear and there were few pyknotic nuclei. In view of the changes in the erythropoietic tissue and of the subsequent response to liver, it is interesting that the fractional test meal revealed achlorhydria; unfortunately the effect of histamine was not observed.

Failure with Nucleotide Therapy

It was concluded that the patient was suffering from a chronic form of agranulocytosis, possibly the effect of

the amidopyrine and gold which he had received. In previous work on agranulocytosis (Witts, 1936) we had had troublesome reactions on treatment with pentnucleotide. Pentnucleotide is an approximately equimolecular mixture of the sodium salts of the four nucleotides obtained by the hydrolysis of yeast nucleic acid. These nucleotides are all compounds of bases with *d*-ribose and phosphoric acid. The four nucleotides are: adenylic acid (adenine ribo-phosphoric acid), guanylic acid (guanine ribo-phosphoric acid), uridylic acid (uracil ribo-phosphoric acid), and cytidylic acid (cytosine ribo-phosphoric acid). Of these nucleotides the first two are derived from purine bases and the second two from pyrimidine bases. Dr. A. L. Bacharach suggested to us that, in view of the pharmacological action of adenosine on the cardiovascular system, it was possible that the adenylic acid was responsible for the reactions occurring after injection of pentnucleotide and that they might be avoided by omitting the purine derivatives. The Glaxo Laboratories kindly supplied us with an equimolecular mixture of the two pyrimidine nucleotides, cytidylic and uridylic acids. It was put up in the same concentration as pentnucleotide, 0.7 gramme per 10 c.cm. Ten cubic centimetres were injected twice daily for six days, but there was little effect on the total or the differential white cell count. After a few days' interval the patient was treated with pentnucleotide in doses of 10 c.cm. twice daily intramuscularly for nine days; this too failed to produce any increase in the white count or the polymorphonuclear cells. Neither the pyrimidine nucleotides nor pentnucleotides gave any troublesome reactions in this patient.

Results of Liver Treatment

Nucleotide therapy having failed, the patient was treated with liver extract (hepatex), which was given in doses of 2 c.cm. twice daily intramuscularly. An improvement in

treatment, though it was still below the normal limit, and large mononuclear cells, which had constituted about 20 per cent. of the white cells, fell to about 6 per cent. at the end of the treatment. The total white cells, neutrophils, and weighted mean are shown graphically in the chart. Sternal puncture was done again at the end of liver treatment, when a preponderance of polymorphonuclear leucocytes was found and the differential count was as follows:

Myeloblasts	4%	Eosinophils	1%
Premyelocytes	2%	Lymphocytes	10%
Myelocytes	11%	Monocytes	0.5%
Metamyelocytes	6%	Reticulum cells.. ..	0.5%
Staff neutrophils	35%	Macroblasts	3%
Segmented neutrophils	14%	Erythroblasts	12%
Basophils	0%		

From the examination of the blood and of the sternal puncture material the patient now appeared to be in a normal haematological state, but his dimness of vision persisted. It was decided, by giving a therapeutic dose, to find out if he was susceptible to amidopyrine. With this view the diurnal variation of the leucocytes from 10 a.m. to 6 p.m. was first observed, the patient being kept in bed during the whole time but having the usual diet. Next the effect of a single dose of amidopyrine and of three successive doses of the drug were noted. No immediate effect on the total white cells and the neutrophils was apparent after single or repeated doses, though there was a suggestion of a slight delayed action. As the patient had had injections of gold for his eye trouble the effect of 0.1 gramme of solganol intramuscularly was noted. The white cells fell from an unusually high level of 9,200 (neutrophils 6,800) to a minimum of 5,000 (neutrophils 2,000) six hours later, and they remained at a lower level than previously for the remainder of the period of observation. It is doubtful, however, whether

the total white cell count and the neutrophils was noticed on the fifth day; this improvement continued and reached a maximum on the thirteenth day of the liver treatment, when the total white cells had risen from 3,800 to over 7,000 per c.mm., of which more than 5,000 were neutrophils. Liver treatment was continued for thirty-five days, during which time the total white cells fluctuated between 6,000 and 7,000 per c.mm., with a total neutrophil count of 4,000 to 5,000 per c.mm. The weighted mean of the nuclear lobes in the Arneth count, which was very low to start with, was much higher at the end of the liver

the fluctuations in the white cells were attributable to the amidopyrine and the gold, as they can be equally well explained by the instability of a marrow which had so recently been stimulated to activity after a long period of torpor. Further experiments were impossible, as the patient was naturally anxious to return home after his long stay in hospital. In November, 1936, his eyes were a little better, and the white cells were 7,600 per c.mm.

He was seen again in May, 1937. He was much better in himself, but there was no change in the eyes, and the iritis continued to flare up at intervals. He had had

no treatment except atropine drops. The blood had been examined several times and found normal. The count on May 4, 1937 was: red cells, 4,940,000 per c.mm.; haemoglobin, 110 per cent.; white cells, 7,100 per c.mm.; colour index 1.1. The differential white count was: lymphocytes 14 per cent., polymorphs 77 per cent., eosinophils 1 per cent., basophils 1 per cent., metamyelocytes 2 per cent., and monocytes 5 per cent.

We do not know why some patients with agranulocytosis respond to nucleotide, others to liver, and others again to neither of these substances. In acute cases, most of which are due to sensitivity to amidopyrine, the predominant cell in the marrow is the myeloblast or stem cell. It is in cases of this kind that nucleotide has had most success. Our patient's illness was chronic, and the development of his white cells was apparently arrested at the myelocyte level. He responded to liver but not to nucleotide. It may be, then, that the results of treatment are to some extent determined by the level at which leucopoiesis is arrested, but our data on these matters are still too fragmentary to be regarded as reliable evidence.

Summary

A man who had suffered for five years from an unexplained iridocyclitis was discovered during the course of a routine investigation to have a mild chronic agranulocytosis. Sternal puncture revealed arrest of maturation of the myelocytes in the bone marrow. The patient had taken amidopyrine and gold in the past, but no clear evidence of sensitivity to either of these drugs was obtained. There was no response to pyrimidine nucleotides or to pentnucleotide, but on treatment with intramuscular liver extract the white cells returned to normal levels and the bone marrow was restored to normal. The blood has remained normal without further treatment, but the iridocyclitis has not greatly improved.

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L. J. Lindström (*Finska LäkSällsk. Handl.*, March, 1937, p. 207) calculates that from 2 to 3 per cent. of all males suffer from undescended testicle, and that at least thirty different operations have been devised for its cure. At the Vasa Hospital he has practised the operation devised by the American Torek on seven patients whose ages ranged from 1½ to 33 years. One of the patients, aged 22, was so pleased with the results of the first stage of the operation that he refused the second stage as superfluous. In every case the wounds healed by first intention, the testicle remained within the scrotum, and the patient was very pleased with the final results. At the first stage of the operation the testicle is detached from the surrounding structures, the cord being freed from fibres of muscle and connective tissue and the pampiniform plexus. After the testicle and scrotum have been secured to the inner side of the thigh the second stage of the operation is undertaken from four to six months later, and the testicle and scrotum are secured in the normal position. For children it may be well to give hormone treatment as a preliminary to the operation, which should preferably be undertaken at the age of 12 to 14 if a hernia or other complication has not required an earlier intervention. Waiting till puberty may render any operation superfluous; and in this connexion the author refers to the experience of Bjerke, who in 1935 gave an account of 188 Danish boys with undescended testicle. In 63 per cent. spontaneous descent occurred, the arrival of the testicle within the scrotum taking place in most cases between the ages of 10 and 15.

CANCER OF OESOPHAGUS TREATED BY DEEP X-RAY THERAPY (SYMPTOM-FREE NEARLY TWO YEARS)

BY

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This brief communication refers to a patient in whom cancer had developed in the mid-thoracic region of the oesophagus. The case-history seems worthy of publication because the method employed by Dr. Levitt (*vide infra*) for distal irradiation of the lesion was followed by a much longer freedom from recurrence than had hitherto come within my personal experience. This had been limited to local therapy, which during the past ten years or so involved the implantation of platinum-screened needles containing radium element or its emanations in glass "seeds."

It is scarcely necessary to add that, by direct oesophagoscopy, these were inserted into the visible growing margins of the lesion and its deeper peripheral extensions in so far as these could be gauged by careful inspection of the diagnostic x-ray film. Perhaps it may be permitted me to state that having been associated with the Radium Institute since its foundation in 1910, an exceptional amount of material has been at my disposal for testing various techniques which, each and all, have aimed at providing uniform and efficient irradiation of oesophageal cancer. Yet in spite of such advantages the results have been very disappointing. I cannot recall to mind a single patient who did not succumb to the disease within twelve months from the commencement of treatment.

In making this statement it would be only fair to add that a large majority of those patients belonged to the poorer classes and did not seek relief from their chief symptom, dysphagia, until the primary lesion was far advanced and not infrequently associated with near or distant secondary deposits. In such circumstances it was only possible to destroy the obstructive portion of growth and thereby restore the power of swallowing. As might be expected, considerably longer respites were afforded to patients more happily situated provided that their lesion was treated in its earlier phases. But even so, I think it will generally be agreed by experts that luck has played a considerable part when a patient has enjoyed a comparatively long freedom from recurrence, because this implies that, by mental visualization alone, the surgeon has been fortunate enough to implant the radium needles in the deeper, peripheral, and actively growing areas of the growth (*vide* H. S. Souttar, *British Medical Journal*, May 1, 1937). On the other hand, it cannot be denied that those who have mastered the technique of local irradiation will secure better results than the occasional operator—which seems to support the definition of "luck" as "an accident which rarely happens except to the competent."

Be that as it may, I had seen a few patients who, after treatment by deep x-ray therapy, had secured far longer periods of freedom from recurrence than any obtained by me with local irradiation, and the following case-history seems to warrant the advice which was given to the patient.

Clinical Record

H. S., aged 75, was referred to me on July 7, 1934, with the history of "difficulty in swallowing," which had been slowly increasing since it was first noticed some three